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TECHNICS FOR MINIMIZING TRAUMA TO THE TRACHEOBRONCHIAL TREE AFTER TRACHEOTOMY*

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OBSTRUCTION of the upper respiratory airway due to laryngopharyngeal paralysis is frequent in acute poliomyelitis, extensive polyneuritis, head injuries, myasthenic crises or coma induced by drug poisoning. Coughing force is impaired, and cough reflexes are often depressed. A tracheotomy relieves the upper respiratory obstruction, but the tracheobronchial tree must then be aspirated directly through the tracheotomy to keep the lower airway patent. Under these circumstances, tracheobronchial secretions often increase markedly during the first few hours after tracheotomy. Blood-tinged aspirate is sometimes observed for several days after surgery when repeated suctioning is carried out. Tracheobronchitis often ensues. Antibiotic-resistant bacterial pathogens are responsible for many of the infections, making treatment particularly difficult.[1] Excessive tracheobronchial secretions, tracheobronchitis and contamination by resistant bacteria all create respiratory obstruction at a deeper level of the tracheobronchial tree that cannot be completely removed through the tracheotomy. Atelectasis and bronchopneumonia result and induce systemic hypoxia and hypercarbia, which threaten further an already damaged or depressed nervous system.

To determine whether any of the complications after tracheotomy were preventable, our own tracheotomy-care program in the neurologic unit and the respirator center was very carefully reviewed. Twenty-five patients on the general medical and surgical services throughout the hospital who had had tracheotomies were also observed to determine the usual methods of tracheobronchial care. The tracheobronchial trees and lungs of 8 consecutive patients who had died after tracheotomy were studied at autopsy. Subsequently, a method of suctioning was devised and both experimentally and clinically evaluated in an effort to reduce tracheobronchial trauma.

Attention was also given to the problems of long-term tracheotomy care. Some patients with paralytic respiratory failure, particularly poliomyelitics, cannot have their tracheotomy tubes removed immediately after acute illness because of prolonged breathing and swallowing difficulties. Prosthetic plugs, therefore, were designed for 9 patients to permit withdrawal of tracheotomy tubes while the tracheal stoma was maintained for direct access to the tracheobronchial tree.

TRACHEOBRONCHIAL SUCTIONING METHODS COMMONLY USED

Suctioning technics used by either nurses or resident physicians and the depth to which the suction catheter was inserted depended somewhat on the disease for which tracheotomy had been carried out. In patients with impaired cough, deep suctioning (with the catheter introduced more than 10 cm. into the tracheobronchial tree) was common. No. 12-14 blunt-tipped rubber catheters were generally used, and continuous suction pressures were usually set at 25-38 cm. of mercury, although pressures as high as 50 cm. were sometimes employed. Many attendants failed to recognize the hazards of bacterial crosscontamination and kept nasal and tracheal catheters in the same container. In some cases catheters that had been dropped onto dusty surfaces were reinserted into tracheas. Personal hygiene — that is, washing the hands thoroughly between suctioning procedures — was often neglected by attendants.

Most workers wet catheters in water or saline solution before introducing them into the tracheobronchial tree. This was not universal, however, and catheters were sometimes taken directly from dry towels and inserted boldly into tracheotomies. The nurse or doctor usually turned on the suction pump, introduced the catheter through the tracheotomy and advanced the catheter to varying depths of the tracheobronchial tree, often until resistance was encoun-

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tered. The catheter was then often left in position for as long as mucus could be aspirated, and in many cases was vigorously thrust back and forth within the tracheobronchial tree in an effort to increase the yield of aspirate. Patients sometimes became cyanotic during this period. When the suction catheter adhered to the respiratory mucous membrane, it was pulled directly away and then readvanced with no interruption of suction. These maneuvers were tantamount to a crude biopsy technic, for the aspirate often became bloody and small pieces of tissue were sometimes returned. Pressure gauges on suction machines recorded an increase in vacuum of 13-20 cm. of mercury when the catheter adhered to the tracheobronchial wall, increasing the potential trauma of the method. A few nurses pinched off the tube to the aspirator in an effort to minimize trauma before introducing the catheter into the tracheotomy. This also created a greater vacuum of 25-38 cm. of mercury so that catheters often adhered immediately to mucous membranes when the pinch was released. In cases requiring deep suction after recent tracheotomy, tracheal secretions were seldom free from blood staining during the first forty-eight hours after operation. Pieces of tissue were seen in the aspirate, perhaps 70 per cent of the time. Few nurses or residents were aware that either of the main-stem bronchi could be entered selectively by turning the chin to the opposite shoulder before introducing the catheter. Thus, the left main-stem bronchus was often filled with secretions when the airway was checked for patency by the reviewing physician.

It was also noted during this study of tracheotomy care that nasal and oral suctioning was roughly performed by several attendants. Swollen edematous uvulas, bleeding noses and edematous, mucus-covered, injected pharynges ensued. These changes increased the likelihood of upper respiratory obstruction and contributed to the need for tracheotomy in some patients with swallowing or respiratory paralysis.

Pathological Changes in the Tracheobronchial Tree after Routine Tracheal Aspiration

The tracheobronchial trees of 8 patients who died eighteen to ninety-six hours after tracheotomy were examined. Three patients died of barbiturate poisoning, 2 of pulmonary emphysema and bronchitis, and 1 each of liver coma, head injury and postoperative pneumonia. Tracheotomy in each patient had been followed by at least hourly tracheobronchial suction. The entire tracheobronchial tree and lungs were removed en bloc, including the site of the tracheotomy, with the tracheal cannula usually in situ. After gross inspection and description, cross-sections were taken, imbedded in paraffin, stained with hematoxylin and eosin and examined microscopically.

Pathological findings in all 8 patients were similar, differing only in degree. In each case the inner wall of the trachea was grossly hemorrhagic and swollen from the end of the tracheotomy tube to the carina. The right main-stem bronchus showed similar changes down to the point where it divided in the right lower lobe. The surface of the mucous membrane was comparatively lusterless and usually covered with a moderate amount of hemorrhagic exudate. Five of the 8 specimens contained acute, gross ulcers on the posterior or lateral walls of the trachea starting at the lower level of the tracheal cannula and extending for 1 to 3 cm. in length. One patient had grossly visible ulceration of the right main-stem bronchus. The left main-stem bronchus in 6 cases was filled with blood-tinged mucopurulent exudate, but the underlying mucous membrane appeared normal; the mucous membranes in the other 2 were moderately injected and swollen. Six patients had purulent bronchopneumonia with extensive purulent tracheobronchitis distal to the main-stem bronchi.

Microscopical sections of trachea and right main-stem bronchi in all specimens demonstrated extensive damage to mucous membranes and submucosa. The left main-stem bronchi had slight or no changes except for mucopurulent exudates in the lumens of all. In many sections the tracheal epithelium was completely denuded, and it was unusual to find more than approximately 40 per cent of the epithelium intact in any tracheal section below the inner orifice of the tracheotomy tube. Areas that did not appear ulcerated on gross examination had frequently lost their epithelial covering, and the submucosa was edematous, hemorrhagic and heavily infiltrated with acute inflammatory cells. The regions of grossly visible ulcerations showed more extensive microscopical changes. Here, both epithelium and submucosa were completely eroded in some places, only a layer of red cells and inflammatory exudate remaining adjacent to cartilage or muscle. Such deep ulcerations blended into the adjacent less damaged areas with irregular margins, the entire section usually showing severe destruction (Fig. 1). Peritracheal and peribronchial inflammation was observed in these cases.

"Regulated-Pressure" Method of Tracheal Suctioning

This modification of tracheobronchial suctioning was devised in an effort to reduce the mucous-membrane damage described above. The method is partially shown in Figures 2-4, which are separated parts of instructions posted by the bed of every patient who has just had a tracheotomy. A Y tube was inserted into the suction line so that vacuum could be released immediately by finger-tip control. Firm-rubber No. 12 whistle-tip catheters were lubricated in 5 per cent sodium bicarbonate solution, and emphasis was placed on scrupulous cleanliness and keeping nasal and tracheal catheters separate. Nurses and physicians were instructed to insert catheters into the tracheotomy and to guide them into right or

left main-stem bronchi by turning the chin to the opposite shoulder. The Y valve was left open during insertion, and catheters were introduced to the full depth of the bronchi. Catheters were then withdrawn 1 or 2 cm., to remove the tip from mucous membrane, before the Y valve was closed with the finger tip and suction applied. Whenever a catheter sucked tightly against mucous membrane, the vacuum was externally released through the Y valve before the catheter was drawn away from the tracheobronchial wall. Catheters were slowly withdrawn with a rotary movement, pressures being carefully controlled with the finger tip on the Y valve. Each aspiration was limited to fifteen seconds. Unless secretions were so voluminous as to threaten asphyxia, three minutes' rest was allowed between aspirations so as not to induce hypoxia.

FIGURE 1. *Cross-Section of Human Trachea 4 Cm. below the End of the Tracheotomy Tube (X13).*
The mucosa has been completely replaced by inflammatory exudate in the right side of the section, and fragmentation with inflammatory infiltration marks the remainder of the mucosa.

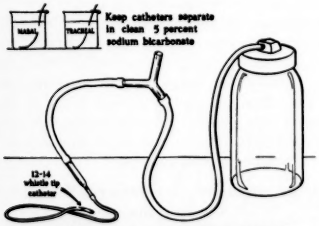
NASAL
TRACHEAL
Keep catheters separate in clean 5 percent sodium bicarbonate
12-14 whistle tip catheter
SUCTION EQUIPMENT WITH "Y" FITTING FOR FINGER-TIP VACUUM CONTROL

FIGURE 2. *Portion of Chart, Showing Equipment.*

COMPARISON OF SUCTIONING METHODS IN LABORATORY ANIMALS

Eleven cats weighing approximately 4 kg. were anesthetized with pentobarbital sodium, tracheotomies performed, and No. 3 tracheotomy tubes inserted. A standard hospital suction machine was set at a pressure of 20 cm. of mercury and connected to No. 10 whistle-tip rubber catheters having accessory side lumens 2 cm. from the catheter tips. Experiments were carried out on three different days. In each experiment 1 cat was tracheotomized as a control and received no suction. The other animals were divided evenly, 4 being suctioned by the technic commonly observed on the wards (called the "observed" method in this experiment) and 4 by the "regulated-pressure" technic described above. Each of the 8 cats were suctioned every fifteen minutes for eight hours. Half the suctioned animals were killed immediately at the end of the experiment, and the other half sixteen hours later. Two controls were killed at the end of experimental periods; 1 was kept for sixteen hours. The tracheobronchial trees and lungs of all animals were dissected, examined grossly, photographed and sectioned extensively for microscopical examination.

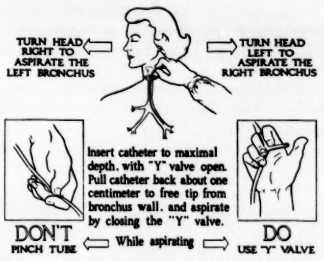
TURN HEAD RIGHT TO ASPIRATE THE LEFT BRONCHUS
TURN HEAD LEFT TO ASPIRATE THE RIGHT BRONCHUS
Insert catheter to maximal depth, with "Y" valve open. Pull catheter back about one centimeter to free tip from bronchus wall, and aspirate by closing the "Y" valve.
DON'T PINCH TUBE
While aspirating
DO USE "Y" VALVE

FIGURE 3. *Insertion of Catheter Demonstrated on Instructions Posted by the Bed after Tracheotomy.*

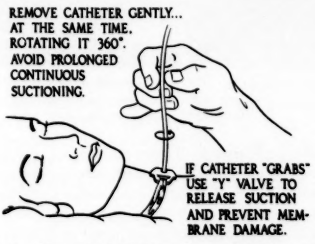
REMOVE CATHETER GENTLY... AT THE SAME TIME, ROTATING IT 360°. AVOID PROLONGED CONTINUOUS SUCTIONING.
IF CATHETER "GRABS" USE "Y" VALVE TO RELEASE SUCTION AND PREVENT MEMBRANE DAMAGE.

FIGURE 4. *Removal of Catheter Demonstrated on Instructions Posted by the Bed after Tracheotomy.*

All animals had moderate amounts of watery, blood-tinged mucus aspirated from the tracheobronchial trees during the first postoperative hour or two. After this, however, bloody mucus disappeared in all animals except for 1 of those aspirated by the observed technic. By the end of the fourth hour, and

thereafter, little or no mucus could be aspirated from the animals treated with regulated-pressure suction, whereas 3 to 5 ml. was consistently returned from the group being treated with the observed technic. Blood-tinged aspirate reappeared at six hours in 2 cats being aspirated by the observed technic, and thickened yellow blood-tinged secretions were aspirated from 3 of the 4 cats by the end of the experimental period.

The differences in gross appearance between the tracheobronchial trees of cats treated by observed suction and those receiving the regulated-pressure method was striking (Fig. 5). Mucous membranes of the former group were hemorrhagic, edematous and often ulcerated. These changes extended from the level of the end of the tracheotomy tube down to the point where the right main-stem bronchus had become too small to pass the catheter. The animals receiving observed suction, and kept overnight before being killed, had moderate to marked mucopurulent secretions coating the trachea and both main-stem bronchi. The tracheobronchial trees of the regulated-pressure-treated animals, by contrast, were moderately injected, showed little edema and were not ulcerated. The 2 animals in this group kept overnight had moderately dry mucous membranes, with mild mucopurulent exudates chiefly collected in the left main-stem bronchi. Control animals showed petechial hemorrhages under the sites of tracheotomy tubes and moderate drying of the tracheobronchial mucous membranes but no other changes.

Microscopical abnormalities were significant in the tracheobronchial trees of both the group treated by observed and that treated by the regulated-pressure method of suction. Epithelial erosion occurred in both groups. Erosion was greater in degree in the cats treated by observed suction, in which almost no tracheal epithelium remained. Submucous inflammation was present in both groups, but only the animals aspirated by the observed method showed extensive fragmentation or disappearance of submucosa; hemorrhagic submucosal infiltration was heavier in this group. The 2 cats treated by observed suction and kept for sixteen hours both had peribronchial pulmonary inflammatory changes. These were not found in other animals. The proximal part of the right main-stem bronchus suffered the greatest damage in both groups of suctioned animals; in the regulated-pressure-treated group approximately 50 per cent of the respiratory epithelium remained on a generally intact basement membrane whereas in the animals suctioned by the observed method, the entire mucous membrane was usually eroded down to the basal mucous glands or muscularis. Inflammatory exudate was revealed in the lumens of the tracheobronchial trees in both groups of suctioned animals about equally on microscopical examination. No significant changes were observed distal to the tracheotomy tube in the controls except for scattered epithelial fragmentation and small amounts of blood in the tracheobronchial lumens.

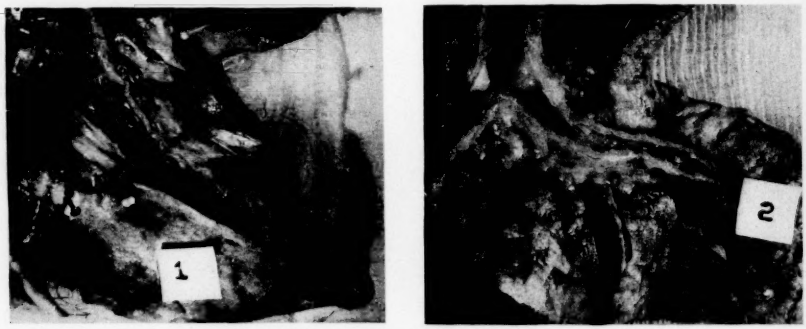

FIGURE 5. *Effects of Tracheobronchial Aspiration on Cats.*
1=*right main-stem bronchus and lower trachea of an animal treated by observed suction.*
2=*right main-stem bronchus and lower trachea of an animal treated by regulated-pressure suction.*

USE OF THE REGULATED-PRESSURE METHOD ON CLINICAL SERVICES

To try to reduce excessive trauma during suction, the instructions shown separately in Figures 2-4 were mounted together on cardboards, 36 by 46 cm., and hung in nursing stations in the poliomyelitis respirator center, in the acute-neurologic-disease ward and in the acute-infectious-disease ward. When patients received a tracheotomy or were placed in respirators, a poster was placed by the bedside, and methods of suction reviewed with each new house officer, medical student or nurse at the beginning of his tour of duty. The importance of strictly aseptic tracheotomy care and the susceptibility of the open

trachea to infection was emphasized. Air inspired into tracheotomies was humidified by connection of a jet nebulizer containing warmed saline solution to an oxygen tank, and the nebulized stream was directed at the tracheotomy orifice.

Fourteen patients (8 with poliomyelitis, 4 with barbiturate poisoning and 2 with polyneuritis) have had tracheotomies since the program described above was started. Hemorrhagic tracheal aspirates disappeared within twenty-four hours of operation in all. In 2 patients bronchopneumonia developed (1 of these had aspirated a tube feeding). Extensive tracheobronchitis or long-continued postoperative secretions were not a problem in the remaining 12. Only 1 patient who was treated with regulated-pressure suction during his life has been autopsied. This man, with a fulminating peripheral neuropathy and viral hepatitis, had a tracheotomy thirty-four hours before he died. He required tracheobronchial cleansing approximately every forty-five minutes after tracheotomy. Grossly, at post-mortem examination, the tracheobronchial tree was injected but not heavily hemorrhagic. No ulcerations were present, and exudate was thin and mildly blood tinged. Microscopical sections showed slight epithelial destruction, with little submucosal inflammatory damage. The lungs were free of infection.

Replacement of Tracheotomy Tubes by Inert Plugs in Patients with Chronic Paralytic Respiratory Failure

Many patients with poliomyelitis who are in respiratory failure regain breathing function either slowly or incompletely. Patients with myasthenia gravis or polyneuritis may be similarly limited. Heavy tracheobronchial secretions of mucus often persist in those who have received a tracheotomy, and intermittent suction is required for weeks or months after acute illness. Metallic tracheotomy tubes create at least part of the irritation that stimulates this heavy production of mucus. Also, tracheotomy tubes make swallowing and learning glossopharyngeal breathing[2] more difficult. Abrupt removal of the tube results in consequent closure of the tracheostoma within twenty-four hours or less in most patients. This is not safe for those who cannot cough and whose airway has been kept patent only by repeated suction. Patients who have had recurrent lung infections or those with swallowing difficulties who are apprehensive about the hazards of choking are reluctant to have the safety factor of their tracheostomas removed. Thus, tracheotomy tubes, though recognizably irritating, are often left in place indefinitely because the danger of their removal outweighs their disadvantages. We have attempted to solve this problem for some patients by inserting a plug to keep the tracheostoma open after removing the tracheotomy tube.

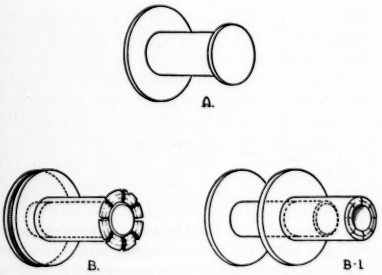

FIGURE 6. *Tracheostomal Plugs.*
A=*solid plug to replace No. 4 tracheotomy tube.* B=*two-piece plug of same size (note that when the obturator is withdrawn, the endotracheal flange retracts, permitting insertion or withdrawal of plug; when the obturator is inserted, the flange expands, preventing extrusion of the plug through the stoma).*

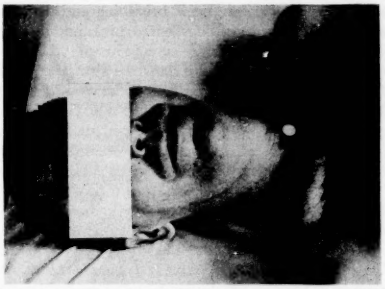

FIGURE 7. *Teflon Plug Substituted for No. 5 Tracheotomy Tube in Patient R. F.*

Several types of plugs have been devised in an effort to find a nonirritating, self-retaining device that would fit into the tracheostoma and not obstruct the airway.* The present forms of these are shown in Figure 6. The plugs are turned from Teflon (polytetra-fluoroethylene) rod stock, have shaft diameters equal to sizes No. 2, 3, 4 and 5 tracheotomy tubes and shaft lengths varying from 0.8 cm. to 1.9 cm. Teflon is nonwettable, and experimentally evokes minimal tissue reaction.[3] The plugs can be boiled, washed or soaked in antiseptic without harm. The plugs are opaque, white, unobtrusive and cosmetically satisfactory to patients (Fig. 7).

Plugs are substituted for tracheotomy tubes as early as possible in convalescence, when pulmonary infection has largely subsided or repeated choking during swallowing efforts has ceased. The tracheotomy tube is removed and the distance from the anterior tracheal mucous membrane to the skin is

*Developed in conjunction with Mr. Wayne E. Quinton, Medical Instrument Shop, University of Washington.

measured with a specially designed metal rule.* A solid plug (Fig. 6*A*), with a shaft diameter corresponding to the tracheotomy tube and a shaft distance of 0.2 to 0.3 cm. greater than the length of the stoma, is then inserted. Patients must be watched closely during the first twenty-four hours of plugging, for if the plug becomes extruded and is not immediately replaced, the tracheostoma rapidly constricts. If the solid plug is extruded by the patient during swallowing, glossopharyngeal breathing and so forth, one of the two-piece plugs with spreading internal flanges is substituted (these are not used first since they are more difficult to construct and thus far have had to be made to individual specifications).

Nine poliomyelitic patients with severe paralysis of either breathing or swallowing muscles or both have had their tracheotomy tubes replaced by Teflon plugs up to the present. Clinical data and the effect of plugging on these patients is summarized in Table 1. Two of the patients (S. W. and V. B.), neither of whom has any spontaneous breathing function, have had plugs in place for ten and twelve months respectively. Both claim that they are unaware of the plugs in their necks; both have maintained tracheostomas through which tracheotomy tubes could easily be reinserted during infections, and both have been able to learn glossopharyngeal breathing now that their tracheotomy tubes have been removed. Secretions subsided so promptly in 4 patients (Table 1) that it was possible to close the tracheostomas within two weeks of plugging. Each of these 4 improved so much in ability to cough after the tracheotomy tube had been removed that accumulation of secretions during future infections was an insignificant hazard.

The present forms of plugs could not be retained by 2 patients. Several different plugs had to be tried in 2 other patients before satisfactory fitting was achieved. Additional designs are being developed in an effort to find tracheostomal plugs that will be applicable to all patients with tracheotomies.

*Developed in conjunction with Mr. Wayne Quinton, Medical Instrument Shop, University of Washington.

TABLE 1. *Clinical Data on Patients Using Tracheostomal Plugs.*

PATIENT	AGE	DURATION OF TRACHEOTOMY	FREQUENCY OF SUCTIONING		COMMENT
			BEFORE PLUGGING	AFTER PLUGGING	
	yr.				
L.M.	3½	2 yr.	6–10/night	0	Moderately severe paralysis of face, jaw & swallowing; use of plug eliminated need for nocturnal suctioning & thus of home night nurse; stoma could be closed 2 wk. after plugging.
J. G.	4	4 wk.	3–4/hr.	0	Cessation of tracheal secretions after plugging enabled tracheostoma to be closed in 4 days.
V. J.	7	3½ mo.	6/24 hr.	0	Cessation of tracheal secretions after plugging enabled tracheostoma to be closed in 10 days.
S. W.	17	13 mo.	0	0	No spontaneous breathing ability; despite repeated previous efforts, patient able to learn glossopharyngeal breathing only after tracheotomy tube replaced by plug.
F. L.	20	6 mo.	1–2/hr.	0	Extensive bulbar paralysis with swallowing difficulty plus moderately severe respiratory paralysis; after plugging, secretions ceased; no more choking while swallowing, independent breathing increased 200% in 2 wk., & stoma then closed.
J. S.	21	4 yr.	0	0	Vigorous glossopharyngeal breathing had hypertrophied neck muscles; regularly extruded plug when intratracheal pressure built up; no satisfactory plug devised to date.
V. B.	29	8 mo.	2–3/wk.	0	No spontaneous breathing ability; patient able to learn glossopharyngeal breathing only after tracheotomy tube replaced by plug.
R. F.	32	5 wk.	0	0	Severe swallowing & laryngeal paralysis; oral fluid intake rose from 900 to 2800 ml. per 24 hr. immediately after tube replaced by plug.
H. A.	48	17 mo.	3–4/24 hr.	0	Chronic bronchitis; minimal residual breathing ability; dilated and irregularly shaped tracheostoma; patient unable to retain plug, & tracheotomy tube replaced.

DISCUSSION

Destruction of ciliated epithelium removes a physiologic method of eliminating tracheobronchial secretions and predisposes the trachea to obstructive crusting.[4] In addition, the rate of respiratory epithelial regeneration is inhibited by submucosal inflammation.[5] Erosion of tracheobronchial epithelium in the laboratory animals, even after particular efforts were made to cleanse gently the tracheobronchial tree, emphasizes the susceptibility of the respiratory mucous membranes. These changes demonstrate how gentle bedside care must be if maximal advantages of an artificial airway are to be realized.

Mucous-membrane damage and the stimulation of potentially asphyxiating tracheobronchitis are not the only dangers of too vigorous tracheal suction. Elam and his co-workers[6] observed that poliomyelitic patients in respirators sometimes became hypoxic during prolonged continuous suction. Kergin et al.[7] noted the same phenomenon while aspirating the tracheobronchial tree during thoracic surgery. The mechanism by which hypoxia was induced was not discussed, but presumably it resulted from reflex bronchospasm subsequent to stimulation of the tracheobronchial wall. Ulin and his colleagues[8] believe that hypoxia may intensify vagovagal reflexes

from the trachea, leading to cardiac depression. We have seen supraventricular tachycardias begin during tracheal suction in 2 patients with acute poliomyelitis, and in a woman with bulbar poliomyelitis cardiac arrest developed clinically while her trachea was being aspirated. For all these reasons, tracheotomy does not appear to be a measure that enables inexperienced ward personnel to render more effective care to critically ill patients.[9]

Several of the individual steps in tracheotomy care outlined in this paper have been previously reported. Neffson,[10] as well as many others, has stressed the need for gentleness in postoperative tracheotomy care and has emphasized the need for experienced nurses. Hodes[11] pointed out that the right and left main-stem bronchi can usually be entered by catheter if the patient's chin is turned 90° away from the side to be catheterized. Bower et al.[12] emphasized the need to keep nasal and tracheal catheters in separate containers. Humidification is required for all acutely ill patients after tracheotomy to prevent drying of mucous membranes, with resultant obstructing mucopurulent plugs. Recent communications[13,14] have described effective methods for humidifying air inhaled into the tracheotomy. Whether antibiotics or enzymes directly introduced into the tracheobronchial tree reduce pulmonary infection and help liquefy secretions has not yet been answered conclusively.[15,16] It appears that strictly aseptic care is a more important factor in preventing pulmonary infection.[1]

Clinical results are difficult to evaluate when a single feature of bedside care has been emphasized. Introducing a modification of treatment often encourages closer attention to all aspects of care so that variables are hard to control. It is our impression that after tracheotomy, patients have cleaner tracheobronchial aspirations, less bloody aspirate and less severe tracheal reactions when treated with the technics recommended above. Extensive bronchopneumonia, atelectasis and uncontrollable hypoxia have become less frequent. The pathological changes in patients suctioned by the observed method emphasized the need for a more gentle approach; both the bedside observations and the results of the experiments indicate that the regulated-pressure method of cleansing the tracheobronchial tree is superior to those previously in general use.

The prompt reduction in tracheobronchial secretions that followed substitution of tracheostomal plugs for tracheotomy tubes clearly demonstrates how irritating metallic tubes are. The greater ease with which patients learned to swallow and learned glossopharyngeal breathing after the plugs were substituted also indicates that heavy, bulky tracheotomy tubes may impede the return of co-ordinated neuromuscular function in bulbar-innervated muscle groups.

Summary and Conclusions

Tracheotomies are often necessary to relieve obstruction of the upper airway in patients with respiratory failure due to acute lesions of the nervous system. Observation of the methods used to suction the tracheobronchial tree after tracheotomy showed that nurses and resident physicians often had little regard for the fragility of respiratory mucous membranes, and that aseptic technic was often neglected. Tracheobronchitis and long-lasting hemorrhagic aspirates were frequent sequelae to tracheotomy. These complications threatened to produce deep tracheobronchial obstruction that could not be relieved by tracheotomy. The tracheobronchial trees of 8 patients with tracheotomies who had had aspirations by usually observed methods were studied at autopsy. The membranes of the tracheas and proximal right main-stem bronchi were denuded of epithelium, intensely hyperemic and often grossly ulcerated. The left main-stem bronchi were partially occluded with mucopurulent secretions.

A method of tracheobronchial cleansing was devised in an effort to reduce tracheobronchial trauma. Suction was briefly and intermittently applied so as to avoid hypoxia; vacuum pressures were carefully controlled to minimize membrane damage, and gentle guiding and manipulation of catheters was emphasized. Experimentally, this regulated-pressure method was found to cause less tracheobronchial damage than the usual technics of tracheal cleansing. The intensity of post-tracheotomy tracheobronchitis and the duration of hemorrhagic tracheobronchial secretions were reduced when this technic was applied to human patients.

Metallic tracheotomy tubes are irritating to tracheal mucous membranes and impede the return of co-ordinated neuromuscular function in bulbar-innervated structures. Teflon tracheostomal plugs were successfully substituted for tracheotomy tubes in 7 of 9 patients convalescing from poliomyelitis. Secretions requiring repeated aspiration promptly subsided, swallowing and glossopharyngeal breathing were learned more easily, and tracheostomal closure was facilitated after substitution of the plugs. Immediate access to the tracheobronchial tree was thus retained, and the undesirable effects of tracheotomy tubes on tracheal mucous membrane and on bulbar-innervated muscle function were eliminated.

References

1. Lepper, M. H., Kofman, S., Blatt, N., Dowling, H. F., and Jackson, G. G. Effect of eight antibiotics used singly and in combination on tracheal flora following tracheotomy in poliomyelitis. *Antibiotics & Chemother.* **4**:829-843, 1954.
2. Dail, C. W., Affeldt, J. E., and Collier, C. R. Clinical aspects of glossopharyngeal breathing: report of use by one hundred postpoliomyelitic patients. *J.A.M.A.* **158**:445-449, 1955.
3. LeVeen, H. H., and Barberio, J. R. Tissue reactions to plastics used in surgery with special reference to teflon. *Ann. Surg.* **129**: 74-84, 1949.
4. Conley, J. J. Diagnosis and treatment of encrustations in trachea. *J.A.M.A.* **154**:829-832, 1954.
5. Wilhelm, D. L. Regeneration of tracheal epithelium. *J. Path. & Bact.* **65**:543-550, 1953.
6. Elam, J. O., Hemingway, A., Gullickson, G., and Visscher, M. B. Impairment of pulmonary function in poliomyelitis: oximetric studies in patients with spinal and bulbar types. *Arch. Int. Med.* **81**:649-665, 1948.
7. Kergin, F. G., Bean, D. M., and Paul, W. Anoxia during intrathoracic operations: preliminary report. *J. Thoracic Surg.* **17**:709-711, 1948.

8. Ulin, A. W., Olsen, A. K., and Martin, W. L. Factors determining mortality in patients with acute head injury. *J.A.M.A.* **157**:496-499, 1955.
9. Galloway, T. C., and Seifert, M. H. Bulbar poliomyelitis: favorable results in treatment as problem in respiratory obstruction. *J.A.M.A.* **141**:1-8, 1949.
10. Neffson, A. H. Tracheotomy in bulbar poliomyelitis: review. *Am. J. M. Sc.* **224**:465-481, 1952.
11. Hodes, H. L. Personal communication.
12. Bower, A. G., Bennett, V. R., Dillon, J. B., and Axelrod, B. Investigations on care and treatment of poliomyelitis patients: physiological studies of various treatment procedures and mechanical equipment. *Ann. West. Med. & Surg.* **4**:686-716, 1950.
13. Kubicek, W. G., et al. Oxygen therapy in poliomyelitis: tracheotomy inhalator incorporating humidification and optional use of positive pressure for oxygen therapy in patients with tracheotomy. *Arch. Phys. Med.* **29**:217-225, 1948.
14. Denton, R., and Schaeffer, J. N. Continuous oxygen-aerosol for tracheotomized respirator patient. *Arch. Phys. Med.* **33**:727-731, 1952.
15. Steigman, A. J., and Scott, C. H. Trypsin in poliomyelitis patients with tracheotomy. *J.A.M.A.* **150**:1403, 1952.
16. Kofman, S., Lepper, M. H., Jackson, G. G., and Dowling, H. F. Effect of proteolytic enzymes on physical and chemical characteristics of tracheobronchial secretions of patients with poliomyelitis. *Am. J. M. Sc.* **228**:426-431, 1954.

SURGERY OF THE BILIARY TRACT

II. Treatment of Acute Cholecystitis

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THE purpose of this paper is to present the experience at the Massachusetts General Hospital in the treatment of acute cholecystitis from 1943 to 1953 inclusive. During this time the concepts and methods of treatment of this disease have been relatively uniform, and it was believed that valuable information could be obtained from an analysis of this experience. A comparison of the mortality and morbidity resulting from surgical treatment of the acute phase of cholecystitis with that attending similar surgical procedures in the chronic or interval phase of the disease is also given.

MATERIAL

All 716 patients with acute cholecystitis treated from 1943 to 1953 are included in this study. Cases of definite acute pancreatitis, with or without associated acute cholecystitis, have been excluded. In such cases the pancreatitis took precedence in determining the methods of treatment chosen.

Only cases in which the diagnosis of acute cholecystitis was confirmed by pathological examination are included except a few in which a cholecystostomy was done and no tissue was available for examination. In these the gross pathological findings were accepted.

PLAN OF TREATMENT

Any reasonable plan for the management of patients with acute cholecystitis must take into account the nature of the pathologic process. From the evidence now available it appears that acute cholecystitis is caused by the irritating action of some of the constituents of bile and is usually related to obstruction of the cystic duct. Impairment of lymphatic flow and vascular supply may follow, even to the point of gangrene. Infection frequently occurs secondarily and may assume a predominant role.

In the early stages of acute cholecystitis the changes in the gall-bladder wall and in the structures around the cystic and common ducts are chiefly those of edema that do not significantly increase the difficulties of surgical exposure and identification of these structures. As the process progresses increasing vascularity, cellular infiltration and fibrosis add to the technical difficulties encountered. These may advance to a point where anatomic identification becomes difficult or even impossible.

Usually, the technical difficulties are not greatly increased in the first few days of the acute attack. This is not entirely predictable, however, and occasionally advanced inflammatory changes are found within twenty-four or forty-eight hours of the onset of acute symptoms. The leisurely way in which these changes resolve and the manner in which they may persist for many weeks have been emphasized by Ross, Boggs and Dunphy.[1]

In addition to an evaluation of the local process the general condition of the patient has an important bearing on the plan of treatment regarding both the presence of other, unrelated diseases and the systemic reaction to the acute cholecystitis.

Cholecystectomy, with choledochostomy if indicated, is the ideal treatment for most patients with acute cholecystitis just as it is in the chronic stage of the disease. This does not mean that an emergency operation must be performed immediately on admission to the hospital. Most of these patients will benefit from a period of at least a few hours of rest, sedation and fluid and electrolyte replacement; this period of observation will also serve to reduce the chance of diagnostic errors. Longer periods may be required for careful evaluation of concomitant pulmonary, cardiac or renal disease before surgery is undertaken.

The surgeon should not hesitate to curtail the extent of the surgical procedure if the local pathological changes or the condition of the patient during the operation makes this the safer course of action. A cholecystostomy may be a better choice than a

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difficult and more hazardous cholecystectomy even though it has only about a 50 per cent chance of rendering the patient free from future trouble. The penalty of injury to the common duct because of technical difficulties encountered in the operative field far outweighs the danger of recurrent cholelithiasis or a residual common-duct stone, which can be safely removed at a later operation.

Some cases of acute cholecystitis are best treated without operation. Occasionally, a patient is so sick on admission that surgery is out of the question. In other cases, in which the attack is mild and clearly subsiding when the patient is first seen, it may be advantageous to postpone surgery in favor of a planned interval operation. A strong desire on the part of the patient to avoid operation cannot be ignored and may be a factor in the final decision in a few cases. At times advanced age may be the chief reason for avoiding surgery. In other cases the presence of other, unrelated disease may make nonsurgical treatment desirable. Severe cardiac or renal disorders, recent respiratory infection and extreme obesity are examples of such situations.

When the decision is made to treat a patient with acute cholecystitis without surgery in the expectation that it will subside, an alert attitude must be maintained to detect evidence of any advance of the process. If pain fails to subside promptly or if there is increasing tenderness or spasm or a rising temperature, pulse or white-cell count, the advisability of surgical intervention must be reconsidered. When surgery is undertaken because the acute process fails to subside and the patient is a poor risk it may be necessary to limit such surgery to a procedure that will relieve the acute phase of the disease, usually a cholecystostomy, rather than to attempt a more ideal but more hazardous operation. Unfortunately, in some of these poor-risk patients the conditions are such that common-duct exploration is imperative and must be undertaken in spite of the increased risk.

TABLE 1. *Treatment of Acute Cholecystitis.*

FORM OF TREATMENT	NO. OF CASES	PERCENTAGE OF TOTAL CASES
No operation	124	17.3
Cholecystostomy	37	5.2
Cholecystectomy	401	56.0
Cholecystectomy & choledochostomy	154	21.5
Total	716	

If the acute attack subsides promptly, plans for a later interval operation are usually in order unless the patient is such a poor risk that the danger of elective surgery outweighs that of the disease itself.

RESULTS OF TREATMENT

The over-all mortality in this series was 21 deaths in 716 cases, or 3.0 per cent. Of this group of patients, 124 were treated without operation, 37 with a cholecystostomy, 401 with a cholecystectomy, and 154 with cholecystectomy and choledochostomy (Table 1).

No Operation

Of 124 patients with acute cholecystitis who were not operated upon 5 died, giving a mortality rate of 4.0 per cent (Table 2).

In 2 patients who died the acute cholecystitis developed while they were recovering from other operations. One woman eighty-five years of age had an intertrochanteric fracture of the femur nailed. She died five weeks after operation. The presence of a perforated gall bladder with a subphrenic abscess was not recognized until autopsy. The other patient, a seventy-six-year-old woman with Parkinson's disease and a previous coronary occlusion, had a stormy recovery after resection of the terminal ileum for multiple carcinoids with metastases to the regional lymph nodes. Jaundice developed, with some tenderness and spasm in the right upper abdomen. She was thought to have cholangitis although acute cholecystitis was considered as a possibility. Autopsy showed acute cholecystitis with complete common-duct obstruction due to stones.

TABLE 2. *Mortality According to Treatment of Acute Cholecystitis.*

TREATMENT	NO. OF CASES	NO. OF DEATHS	MORTALITY
No operation	124	5	4.0
Cholecystostomy	37	5	13.5
Cholecystectomy	401	5	1.2
Cholecystectomy & choledochostomy	154	6	3.9
Totals	716	21	
Average			3.0

A man sixty-four years of age was admitted to the hospital with a fifteen-hour history of acute right-upper-quadrant symptoms. He had had a previous attack of pyelonephritis and had poor renal function and an elevated nonprotein nitrogen. He was thought to have acute pancreatitis and was treated on this basis. He died three days after admission. Autopsy showed acute cholecystitis, with perforation and subphrenic and subhepatic abscesses.

Another patient, a very obese seventy-two-year-old woman, who had had a previous cerebrovascular accident with considerable residual disability presented an obscure picture on admission and died the next day. The clinical diagnosis was acute cholecystitis. Permission for autopsy was refused, and the diagnosis could not be definitely confirmed.

The fifth death occurred in a seventy-year-old man who was admitted to the hospital in a moribund condition and died an hour later. Autopsy showed acute cholecystitis, with perforation and generalized peritonitis. He had been referred to the hospital

with the diagnosis of a "heart attack." The most interesting feature of his history was that he had been admitted four days earlier to another hospital, where the correct diagnosis was made. He was sent home on a soft diet with instructions to avoid fats. Continuing acute symptoms had led to another hospital admission.

Cholecystostomy

In keeping with the general policies outlined above, this form of treatment was used for poor-risk patients and for those in whom the local process had advanced to a point where simple drainage was deemed the safest procedure.

Of the 37 patients so treated, 5 died, a mortality of 13.5 per cent (Table 2). Two deaths were directly attributable to the disease itself. One patient died nine days after cholecystostomy with a cholecystoduodenal fistula, subhepatic and subphrenic abscesses and generalized peritonitis. A second patient died of bile peritonitis five days after operation. A third patient died of a pulmonary embolism ten days after operation. Another, a seventy-three-year-old woman with arteriosclerotic and hypertensive heart disease, died of cardiac arrest at the end of the operation. The fifth patient had hypertensive cardiovascular disease with an elevated blood nonprotein nitrogen on admission. He died in uremia six days after operation. He died in uremia six days after operation.

TABLE 3. *Nonfatal Complications According to Treatment of Acute Cholecystitis.*

TREATMENT	NO. OF PATIENTS SURVIVING OPERATION	NO. OF COMPLICATIONS	PERCENTAGE OF COMPLICATIONS
Cholecystostomy	32	3	9.4
Cholecystectomy	396	38	9.6
Cholecystectomy & choledochostomy	148	19	12.8
Totals	576	60	
Average			10.4

In addition, 3 patients had nonfatal postoperative complications (Table 3). These were atelectasis, multiple pulmonary infarcts and wound sepsis.

The postoperative hospital stay of patients surviving cholecystostomy varied from nine to forty-four days. The median stay was seventeen days.

Cholecystectomy

In the period studied, 401 patients with acute cholecystitis were treated by cholecystectomy. There were 5 deaths, giving a mortality of 1.2 per cent (Table 2).

Only 2 of these patients were elderly, and in none was death directly attributable to acute cholecystitis.

One, a seventy-six-year-old woman, died of a massive pulmonary embolism five days after operation. Autopsy was not permitted. Another patient, a man seventy-seven years of age, died twenty days after operation of pyelonephritis and aspiration pneumonitis, confirmed by autopsy.

A forty-nine-year-old man with severe angina pectoris was admitted to the hospital with a diagnosis of myocardial infarction. A few days later localized right-upper-quadrant tenderness and spasm developed. An electrocardiogram failed to show changes consistent with myocardial infarction. At laparotomy an acute cholecystitis with perforation was found. A fatal myocardial infarction occurred on the day of operation, and was confirmed at autopsy.

In another case a persistent fall in blood pressure occurred after operation on a forty-six-year-old woman who had previously been in good general condition except for mild asthma. She died three days after operation with acute cor pulmonale. Permission for autopsy was refused.

The fifth fatal outcome was in a woman of fifty-nine who was being studied in the hospital for pain, cyanosis and coldness of the fingers of two weeks' duration. Acute symptoms and signs in the right upper quadrant developed, and a cholecystectomy was done on the same day. The gall bladder was acutely inflamed and some leakage of bile had occurred into the peritoneal cavity. Atrial fibrillation developed, and she died six days after operation. Permission for autopsy was refused.

TABLE 4. *Complications of Cholecystectomy for Acute Cholecystitis.*

COMPLICATION	NO. OF CASES
Wound sepsis	9
Phlebitis	4
Bile peritonitis	3
Pulmonary infarct	4
Fever of unexplained cause	3
Atelectasis	2
Subhepatic abscess	2
Subphrenic abscess	2
Local skin necrosis	1
Residual common-duct stone	1
Urinary retention	1
Prostatic abscess	1
Acute pancreatitis	1
Pyelonephritis	2
Transient jaundice	1
Pulmonary edema	1
Total	38 (9.6%)

There were 38 nonfatal complications in this group of cases, a rate of 9.6 per cent (Table 3). Wound sepsis was the commonest postoperative complication (Table 4). Bile peritonitis occurred in 3 cases. Re-exploration was done on each patient. In 1, an open leaking cystic duct was found. In the other 2, no source of leak was noted, and reaccumulation of

bile did not follow. Acute pancreatitis developed after cholecystectomy in 1 case.

The period of hospitalization after operation for the 396 patients who survived operation varied from five to sixty days, with a median of twelve days.

These results in the treatment of acute cholecystitis may be contrasted with those observed after cholecystectomy in 1280 patients with chronic cholecystitis operated upon in the eleven-year period from 1943-1953.[2] In the chronic group the mortality was 0.6 per cent, and nonfatal complications occurred in 8.9 per cent of patients surviving operation. The median postoperative stay was the same — twelve days.

Cholecystectomy and Choledochostomy

There were 154 patients who had common-duct exploration performed at the time of cholecystectomy for acute cholecystitis — a rate of 26 per cent of all patients operated upon. Of the ducts explored, 43 per cent were found to contain stones.

Six deaths occurred in this series of cases, a mortality of 3.9 per cent (Table 2). The causes of death in these 6 patients are of particular interest. The first, a woman eighty years of age, had had repeated "gall-bladder" attacks for forty years. She was admitted to the hospital thirty-six hours after the onset of acute symptoms and was operated upon five hours later. An acutely inflamed, edematous gall bladder was removed. The common duct was explored because stones were felt in it. The patient died of acute postoperative pancreatitis seven days later. This was confirmed by autopsy.

The second was a seventy-seven-year-old woman who had an eighteen-year history of recurrent bouts of right-upper-quadrant pain, radiating through to the back, that was consistent with biliary-tract disease; a cholecystogram had showed no filling. The acute attack was of three weeks' duration at the time of admission. After a week of careful evaluation she was operated upon. She had acute cholecystitis, and a large gallstone had eroded into the common duct. The operation presented considerable technical difficulty. She gradually failed, and died three weeks later of aspiration pneumonia. An autopsy was performed.

The third case was that of an eighty-two-year-old woman who had had the diagnosis of gallstones established twenty years previously after her first acute attack. The current attack was of four days' duration at the time of operation. In addition to the acutely inflamed gall bladder, stones were present in the common duct, which was explored. Death occurred on the second postoperative day from myocardial infarction, confirmed by autopsy.

The fourth patient, a woman of seventy-four, gave a fifteen-year history of epigastric distress and fatty-food intolerance, with severe epigastric pain for five days. She was jaundiced. At operation the gall bladder was gangrenous but contained no stones. The common duct was explored because of the presence of jaundice and because the duct was dilated to 1.5 cm. in diameter. No stones were found in it. She died nine hours after operation with a clinical picture consistent with either cardiac failure or a pulmonary embolism. Permission for autopsy was refused.

The fifth death occurred in a man, forty-nine years of age, who had had symptoms for ten years that were thought to be due to duodenal ulcer. His first attack of severe abdominal pain had occurred two years previously. At operation an acutely inflamed gall bladder and stones in the common duct were removed. The postoperative course was characterized by a falling prothrombin level, in spite of vigorous vitamin K therapy, hemorrhage from the abdominal wound and into the gastrointestinal tract and, later, the development of jaundice. He died four weeks after operation. Autopsy showed extensive gas-bacillus infection of the liver.

TABLE 5. *Complications of Cholecystectomy and Choledochostomy for Acute Cholecystitis.*

COMPLICATION	NO. OF CASES
Wound sepsis	5
Residual common-duct stone	2
Excessive bile drainage	2
Excessive bile drainage & atelectasis	1
Acute pancreatitis	1
Obstructing duodenal ulcer, pancreatitis & phlebitis	1
Cholangitis	1
Persistent biliary obstruction	1
Bile peritonitis	1
Hemorrhage from wound	1
Atelectasis	1
Transient brachial palsy	1
Involutional melancholia	1
Total	19 (12.8%)

The last patient who died was a thirty-five-year-old woman with severe Cushing disease. She was jaundiced at the time of operation on the sixth day of the acute attack. Because of this the common duct was explored in addition to the removal of the acutely inflamed gall bladder. The gall bladder contained stones, but the common duct did not. She did poorly after operation and died twenty-seven days later in cardiac failure. An autopsy was performed.

Nineteen nonfatal complications occurred in the patients in this group who survived operation, a rate of 12.8 per cent (Table 3). These are listed in Table 5. Again, wound sepsis was the commonest difficulty, and almost all the complications were directly related to the operation.

The postoperative stay for patients surviving operation varied from nine to eighty-one days, with a median of fourteen days.

In contrast to this series of cases of acute cholecystitis, there were 963 patients on whom cholecystectomy and choledochostomy were done, from 1943-1953, for cholecystitis in the chronic or interval stage.[2] The mortality in the chronic cases was 1.8 per cent, and an additional 9.8 per cent of patients had nonfatal complications. Common-duct exploration was carried out in 43 per cent, and, of the ducts explored, stones were found in 38 per cent. The median postoperative period was fourteen days.

Discussion

The mortality of 3.0 per cent for this series of 716 cases of acute cholecystitis falls within the range of most of the recent reports on this subject[3-10] and is just half what it was in this hospital for a ten-year period ending on January 1, 1940, previously reported.[11]

Although the general philosophy of the management of patients with acute cholecystitis may be oriented toward prompt surgery or delayed operative management after the acute attack has subsided, it is clear from the reports of various authors in recent years that there is increasing emphasis on the careful evaluation of each problem and on a plan of treatment modified to fit the particular situation.[3-10] To this we subscribe.

Many patients are best treated by prompt surgery of adequate extent to correct the existing pathologic conditions, but time must be taken to establish the diagnosis as accurately as possible, to evaluate the patient's general condition and to correct fluid and electrolyte deficits. Some patients should be treated without surgery, and others by simple cholecystostomy.

Errors in diagnosis contributed to at least 3 of the deaths in our series. This has also been noted by Buxton, Ray and Coller,[4] Mustard and Custer[10] and Doubilet, Reed and Mulholland.[6] A confusing factor may be the minimal pain shown by some patients, particularly the elderly and debilitated. The danger of exploratory laparotomy for nonsurgical conditions mistaken for acute cholecystitis has been pointed out by Borland and Jaehning.[3] This is particularly true when the patient proves to have infectious hepatitis.

During any period of observation of a patient with acute cholecystitis it is essential that frequent examinations be made for evidence of spreading inflammation. Any signs warning of such changes must not be overlooked or ignored.

As would be expected from the nature of the group of cases selected for cholecystostomy, this method of treatment carried the highest mortality. Cholecystectomy, on the contrary, in properly chosen cases of acute cholecystitis, had the lowest mortality of the various forms of treatment used. When common-duct exploration was necessary, in addition to cholecystectomy, the risk increased threefold. Most of these fatal cases occurred in elderly patients who had had the diagnosis of gallstones made as the result of previous attacks over a period of many years. It seems logical to attempt to prevent such deaths by renewed efforts on the part of the medical profession to educate patients with gallstones to be operated on at an earlier age, when they are in better general condition and before the process is complicated by the passage of stones into the common duct. It will probably continue to be impossible to save some of the elderly poor-risk patients who present themselves with an acute flare-up of advanced biliary-tract-stone disease. Monroe[12] has clearly shown the dangers of gallstones in older patients and the high rate of complications attributable to them; he has taken a firm stand against the "medical management" of these patients.

Common-duct exploration was somewhat less frequent in patients operated on for acute cholecystitis (26 per cent) than in those operated on between attacks (43 per cent). The less urgent indications for common-duct exploration are and should be ignored in the face of increased technical difficulties due to the acute inflammatory process. Wide variations in the indications for choledochostomy in acute cholecystitis now exist, as shown by the great differences in the rate of occurrence of choledochostomy in recent reports. Glenn[8] gave this figure as 8.75 per cent whereas Dunphy and Ross[7] reported it as 42 per cent.

The proportion of common ducts containing stones was slightly higher in patients explored for acute cholecystitis (43 per cent) than in those on whom the operation was done as an interval procedure (38 per cent). Residual stones were shown later in 2 of the ducts that had been explored and in 1 that had not been explored at the original operation.

Since choledochostomy adds considerably to the operative risk and since more than half the ducts explored did not contain stones, there seems little justification for a complacent attitude in this matter. Continued efforts to improve the indications for and technic of common-duct exploration are indicated.

No accidental injury to the bile ducts occurred in the 576 patients in this series who were treated by operation.

Summary

The results of treatment of 716 patients with acute cholecystitis at the Massachusetts General Hospital in the eleven-year period from 1943 to 1953 are reported.

Of this series of cases, 17.3 per cent were treated without operation, 5.2 per cent by cholecystostomy, 56.0 per cent by cholecystectomy, and 21.5 per cent by cholecystectomy and choledochostomy.

Patients treated without surgery had a mortality of 4.0 per cent. Errors in diagnosis contributed to some of these deaths.

The mortality for cholecystostomy was 13.5 per cent. An additional 9.4 per cent of these patients had nonfatal complications, and the median postoperative hospital stay was seventeen days.

In 401 cases treated by cholecystectomy the mortality was 1.3 per cent, and nonfatal complications occurred in an additional 9.6 per cent. The median postoperative stay was twelve days.

Comparable data on 1280 cases of cholecystectomy for chronic cholecystitis in the eleven-year period from 1943 to 1953 showed a mortality of 0.6 per cent, complications in 8.9 per cent and a median postoperative stay of twelve days.

Cholecystectomy and choledochostomy were done in 154 cases of acute cholecystitis, with a mortality of 3.9 per cent and nonfatal complications in an additional 12.8 per cent. The median hospital stay was fourteen days after operation.

Common-duct exploration was done on 26 per cent of all patients operated on, and stones were found in 43 per cent of the ducts explored.

For comparison, similar data are given for cholecystectomy and choledochostomy in 963 cases of chronic cholecystitis from 1943 to 1953. The mortality was 1.8 per cent, and an additional 9.8 per cent of patients had nonfatal complications. The common duct was explored in 43 per cent, and, of the ducts explored, stones were found in 38 per cent. The median postoperative period was fourteen days.

Elective surgery at a younger age and earlier in the course of the disease is urged for patients with gallstones, as a means of reducing the number of deaths from acute cholecystitis.

References

1. Ross, F. P., Boggs, J. D., and Dunphy, J. E. Studies in acute cholecystitis. III. Pathological process in relation to clinical management of disease: fallacy of "critical period." *Surg., Gynec. & Obst.* **91**:271-276, 1950.
2. Bartlett, M. K., and Quinby, W. C., Jr. Surgery of biliary tract. 1. Mortality and complications of cholecystectomy and choledochostomy for chronic cholecystitis. *New Eng. J. Med.* **254**:154-156, 1956.
3. Borland, V. G., and Jaehning, D. Acute cholecystitis: its early treatment: report of 108 cases. *Surgery* **32**:581-590, 1952.
4. Buxton, R. W., Ray, D. K., and Coller, F. A. Acute cholecystitis. *J.A.M.A.* **146**:301-307, 1951.
5. DeCamp, P. T., Ochsner, A., Baffes, T. G., Bancroft, H., and Bendel, W. Timing in surgical treatment of acute cholecystitis. *Ann. Surg.* **135**:734-745, 1952.
6. Doubilet, H., Reed, G., and Mulholland, J. H. Delayed operative management of acute cholecystitis. *J.A.M.A.* **155**:1570-1573, 1954.
7. Dunphy, J. E., and Ross, F. P. Studies in acute cholecystitis. 1. Surgical management and results. *Surgery* **26**:539-547, 1949.
8. Glenn, F. Surgical treatment of acute cholecystitis. *Surg., Gynec. & Obst.* **90**:643-648, 1950.
9. Holden, W. D., Cebul, F. A., and Loughry, C. W. Management of acute disorders of biliary tract. *J.A.M.A.* **148**:879-884, 1952.
10. Mustard, R. L., and Custer, H. R. Management of acute cholecystitis. *Surg., Gynec. & Obst.* **95**:59-62, 1952.
11. Wallace, R. H., and Allen, A. W. Acute cholecystitis. *Arch. Surg.* **43**:762-772, 1941.
12. Monroe, R. T. *Diseases in Old Age: Clinical and pathological study of 7941 individuals over 61 years of age. (Harvard University Monographs in Medicine and Public Health.* No. 11.) 418 pp. Cambridge: Harvard University Press, 1951. Pp. 202-216.

STAPHYLOCOCCAL ENDOCARDITIS AFTER MITRAL VALVULOTOMY*

Report of Three Cases

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BACTERIAL endocarditis after cardiac surgery has been previously reported in 6 patients.[1-5] Four had undergone mitral valvulotomy, the fifth had a transventricular commissurotomy for aortic stenosis, and the sixth had been operated on for pulmonic stenosis. In 2 of these cases, the organism proved to be an antibiotic-resistant staphylococcus, and the patients succumbed to the infection.[1,2] In a third patient, whose blood culture had yielded a staphylococcus, large doses of penicillin, sulfisoxazole and chloramphenicol resulted in recovery.[3] *Pseudomonas aeruginosa* was recovered from the blood and from the vegetations on the heart valves in the fourth case, reported in England by Brunsdon et al.[4] Two additional patients who were receiving prophylactic antibiotics during the postoperative period had clinical pictures consistent with bacterial endocarditis, but blood cultures were sterile.[5] These 2 patients recovered after intensive antibiotic therapy.

Recently, 3 patients with bacterial endocarditis that followed mitral valvulotomy and was due to an antibiotic-resistant *Staphylococcus aureus* were observed. In a review of staphylococcal endocarditis in 1952, Dowling et al.[6] reported the ratio of streptococci to staphylococci as the causative organisms in bacterial endocarditis as 2.6:1. This is in contrast to the preantibiotic era, in which the *Streptococcus viridans* accounted for about 80 per cent of the cases of bacterial endocarditis.[7] However, it should be noted that staphylococci were cultured from the blood of all 3 of the patients in whom this condition developed after mitral valvulotomy. These 3 cases are being reported to call attention once again to this infrequent but serious complication of commissurotomy as well as to the continuing hazard of infection with antibiotic-resistant micrococci.

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Case Reports

CASE 1. A.K. (M.G.H. 6079), a 36-year-old taxi driver, had been followed at the Massachusetts General Hospital

from his 1st year of life. He had acute rheumatic fever at the age of 8, with recurrences at 11, 13 and 14 years. The murmur of mitral stenosis had been noted since the age of 14. In March, 1953, atrial fibrillation was observed for the 1st time. Six months later, he had an embolus to the right brachial artery. This did not require embolectomy and was followed by a return of good function to the arm. Anticoagulant therapy was maintained thereafter.

On April 26, 1954, the patient entered the hospital because of fever of undetermined origin. Numerous blood cultures were negative, but because of the possibility of subacute bacterial endocarditis, he was given 4,800,000 units of penicillin and 1 gm. of streptomycin daily for 4 weeks. However, he did not become afebrile until the last week of hospitalization, and no definite diagnosis was established. He was discharged on June 18.

There were no febrile episodes during the summer of 1954, but there was a definite increase in exertional dyspnea, and acute dyspnea was noted on several occasions. Because

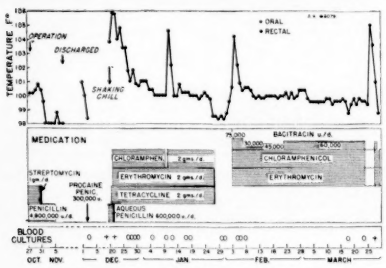

FIGURE 1. *Clinical Course in Case 1.*

of the increasing dyspnea and the previous history of peripheral embolization, mitral valvulotomy was performed on October 27, 1954.*

At operation, a shrunken and fibrous atrial appendage was found to contain an organized thrombus, through which the surgeon's finger was forced with difficulty into the atrium. Tight stenosis was not present, but there was an inelastic calcific plaque on the aortic cusp of the mitral valve. The forefinger could be passed the length of the distal interphalangeal joint without difficulty. Dilatation was accomplished, with splitting of the commissures, and the atrial appendage was excised.

The immediate postoperative course was uneventful. The temperature ranged between 100 and 101°F. by rectum for 4 days, but was normal thereafter. Beginning the day of operation, the patient was given 200,000 units of aqueous penicillin and 0.25 gm. of streptomycin every 6 hours for 10 days. He was discharged on November 8, and when seen 2 weeks later in the Outpatient Department appeared to be doing well.

On December 2, 2 months after operation, he was seen because of a continuous, dull, nonpleuritic pain in the lower portion of the thorax, as well as slight dyspnea of 2 days' duration. He also had had a brief shaking chill, with a rise in temperature to 101°F. on the previous night. Physical examination was unchanged except for a few rales at the right base. A blood culture taken on this occasion was negative. He was given 300,000 units of procaine penicillin and 2 cc. of Mercuhydrin intramuscularly, with subsidence of temperature and dyspnea within a day. For the next 3 weeks he felt relatively well (Fig. 1).

Because of the sudden onset of another shaking chill followed by a drenching sweat and rise in temperature, he was admitted to the hospital on December 20. On physical examination he was sweating profusely, but did not appear acutely ill. The blood pressure was 110/85, the pulse 150 (atrial fibrillation), and the respirations 36. He was noted to have multiple acneiform lesions of the face and upper trunk, some with small pustular centers, but otherwise no significant changes. There was a Grade 1 diastolic blow along the left sternal border. At the apex, there were a Grade 1 systolic murmur and a Grade 2 diastolic rumble. Blood cultures were drawn, and treatment with 200,000 units of aqueous crystalline penicillin intramuscularly every 8 hours was started. Early that evening a generalized erythematous, macular, slightly pruritic rash was noted. Penicillin was discontinued, and tetracycline, 500 mg. every 6 hours by mouth, was substituted.

The blood cultures taken on admission yielded a coagulase-positive *Staph. aureus* sensitive to chlortetracycline, oxytetracycline, chloramphenicol, tetracycline and erythromycin, but with poor sensitivity to penicillin and streptomycin. Accordingly, 500 mg. each of chloramphenicol and erythromycin every 6 hours by mouth were added to the tetracycline.

On January 10, 21 days later, because of a gastrointestinal disturbance, the chloramphenicol was stopped. The other antibiotics were continued. On the next day a sudden chill and rise in temperature were observed, without change in physical findings. Blood cultures at this time were negative. Chloramphenicol was resumed at the previous dosage of 500 mg. every 6 hours by mouth.

The patient remained asymptomatic until January 27, when it became necessary to discontinue all oral medication because of nausea. On February 1 the temperature again began to rise slowly. On February 4 the patient experienced a chill, followed by a temperature of 104°F. The following regimen was instituted: bacitracin, 25,000 units intramuscularly every 6 hours; and erythromycin and chloramphenicol, 500 mg. of each every 6 hours. Because of a temporary decrease in urinary output and a +++ test for albumin in the urine, the bacitracin dosage was reduced to 30,000 units a day. This was later increased to 60,000 units a day, with no subsequent decrease in urinary output. The nonprotein nitrogen ranged between 37 and 50 mg. per 100 ml., and the urine gave a + to ++ test for albumin for the remainder of the time the patient was on this drug.

This regimen was continued for a total of 7 weeks. There was little change in physical findings except that the previously noted acneiform lesions were observed to involve the trunk more extensively and the systolic murmur at the apex was thought to be somewhat louder. The spleen did not become palpable. Early in the evening of the day therapy was discontinued (March 23) there was a sudden onset of severe, sharp, nonpleuritic pain in the left lower part of the chest, unaccompanied by cough or dyspnea.

On March 26 there was a sudden spike in temperature to 105°F. The patient was found to have a confluent urticaria with periorbital and lip swelling as well as moderate wheezing. Epinephrine and Benadryl were given, with prompt subsidence of the eruption and the wheezing. Later that day he appeared much sicker and became disoriented. Hemorrhagic bullae appeared on the left thigh. Because he was believed to be having an exacerbation of the staphylococcal septicemia, treatment with erythromycin and chloramphenicol (2 gm. intramuscularly and 1 gm. intravenously of each) and bacitracin (60,000 units a day intramuscularly) was reinstituted.

Early on March 27 he became cold, clammy and anuric, with a fall in blood pressure to 80/60. Bacitracin was omitted. Nor-epinephrine and whole blood were given, with a rise in blood pressure and return of urine formation. Blood cultures taken on the previous day again were reported positive for a coagulase-positive *Staph. aureus* that was sensitive to chloramphenicol, erythromycin, tetracycline, chlortetracycline, oxytetracycline and bacitracin, with poor sensitivity to penicillin and streptomycin. On the afternoon of March 29, he suddenly became cyanotic and dyspneic, and died 2 hours later.

At autopsy, the heart, together with a considerable amount of attached fat and surrounding tissue, weighed 550 gm. The left atrium was dilated and hypertrophied; a firmly adherent, yellow, hyalinized mural thrombus was found covering its posterior and lateral wall. The mitral valve was markedly thickened and calcified, with an orifice measuring 1.4 cm. in length and up to 0.4 cm. in width and a free surface 1.3 cm. in length along both the anterior and posterior cusps with an additional, approximately 1-cm. sur-

*Dr. J. G. Scannell performed the valvulotomy on the 3 patients in this report.

gical fracture into each commissure. The posterior commissure was filled with a soft, friable, slightly adherent, pinkish-gray vegetation measuring 1 cm. in diameter (Fig. 2). Direct smear of this showed numerous gram-positive cocci in clusters. A hard, calcified nodule measuring 1 cm. in diameter was found in the valve just distal to the posterior fracture site. The anterior commissure was covered by adherent red fibrin. The mitral chordae tendineae were thickened, fused and shortened, and the right ventricle was hypertrophied.

The aortic valve presented an unusual appearance. In a region where the anterior and left posterior cusps had probably at one time been fused, there was a fenestration measuring 1 cm. across. At their edges, these cusps were adherent for a length of 1.3 cm. with an additional slitlike opening measuring 0.8 cm. along the line of adherence. The tricuspid and pulmonary valves showed no disease.

Scattered throughout the myocardium of all chambers and especially the interventricular septum, there were ill defined, blotchy, yellow-gray areas measuring up to a few millimeters each. There was a severe degree of coronary atherosclerosis.

Microscopically, the mitral vegetation consisted of a mass of fibrin, within which were large, dense clusters of gram-positive cocci. Culture of the heart's blood indicated no growth, but culture of the mitral vegetation grew out alpha-hemolytic streptococci. The posterior commissure showed organization with an acute and chronic inflammatory reaction with large clusters of gram-positive cocci. The anterior commissure demonstrated a similar but less extensive inflammatory reaction with gram-positive cocci. The yellow-gray areas described grossly in the myocardium proved to be acute abscesses with abundant gram-positive cocci. Scattered foci of fibrosis were also found. No Aschoff nodules were present.

The lungs were congested and edematous, with areas of emphysema. Large numbers of hemosiderin-laden macrophages were present. There was slight intimal thickening of the pulmonary arteries. The liver, which weighed 2040 gm., showed necrosis and fatty vacuolization of the central zones. A focal acute abscess was seen in 1 section. The spleen weighed 330 gm.,; it contained numerous recent infarcts. The most striking renal finding was the presence of scattered foci of necrosis involving the proximal convoluted tubules. In these areas, the tubular epithelium was desquamated, and the lumens were filled with granular eosinophilic material. These lesions were not unlike those described by Genkins et al.[8] in a case of acute renal failure ascribed to bacitracin nephropathy. Several small healed renal infarcts were found. The duodenum showed extensive mucosal necrosis with a polymorphonuclear infiltrate and large numbers of cocci.

Case 2. N.O. (M.G.H. 866153), a 44-year-old nulliparous housewife, was first seen at this hospital in December, 1953, complaining of increasing shortness of breath for 5 years.

She had had rheumatic fever at 17 years of age but was then well until the age of 39, when she noted swelling of her abdomen and ankles toward the end of the day. For the next 4 years, she was maintained on a low-salt diet, digitalis, ammonium chloride and mercurial diuretics. Dyspnea limited her to 5 or 6 steps, and her ankles and abdomen swelled in the afternoon. There had been some cough but no hemoptysis or wheezing.

On physical examination the pulse was grossly irregular with a rate of 120. At 90° the neck veins filled 3 cm. above the clavicles with a deep jugular pulsation. The chest was clear. The heart was enlarged. The pulmonic 2d sound and the mitral 1st sound were accentuated. There was a Grade 3, high-pitched, systolic murmur at the apex with a Grade 2 diastolic rumble. There was also a Grade 3, high-pitched, systolic murmur 1 cm. above the xiphoid. The liver edge was palpated 4 cm. below the right costal margin, and there was ++ ankle edema.

X-ray examination showed a cardiothoracic ratio of 17:26.5, with the enlargement mainly in the region of the left atrium and the right ventricle. Intracardiac calcification was noted. An electrocardiogram indicated atrial fibrillation, with a ventricular rate of 120, but the pattern of hypertrophy of the left or right ventricle was not apparent.

The patient was followed in the Outpatient Department over the next 11 months. Despite the fact that she was adhering closely to her diet at home and receiving mercurial diuretics 3 times a week, she required 2 admissions to the hospital for diuresis. During 1 of these admissions, she was thought to have active rheumatic fever, with an elevation of both the sedimentation rate and the antistreptolysin titer.

Because of the intensity of the systolic murmur over the xiphoid and the pulsating liver, it was believed that the main component of the systolic murmur was tricuspid re-

Figure 2. *Gross Appearance of the Heart in Case 1, Showing Vegetations on the Mitral Valve and a Mural Thrombus in the Left Atrium.*

gurgitation rather than mitral regurgitation. Cardiac catheterization showed a right atrial pressure curve in the right atrium consistent with tricuspid regurgitation. The calculated mitral-valve area was 0.4 square cm., assuming that there was no regurgitation. It was believed that surgery offered this patient the only chance for lasting benefit. Therefore, despite the fact that she was a poor risk, she was admitted for surgery.

On admission on November 11, 1954, physical examination was unchanged. An electrocardiogram showed atrial fibrillation, with a ventricular rate of 75. There was an incomplete right-bundle-branch block. She was started on intensive diuretic therapy. On the 10th hospital day for no apparent reason she had a shaking chill in the morning. Physical examination was unremarkable. Three blood cultures (5 flasks) were drawn that later showed either no growth or contaminants. Diuresis continued to be satisfactory, and on the 28th hospital day, a mitral valvuloplasty was performed.

The operative note was as follows:

> The mitral valve would admit a finger tip. There was moderate regurgitation pre-split. The mitral valve was calcified on its anterior leaflet. A moderately good split was obtained by finger fracture only.

On the day of operation chloramphenicol was begun in a dosage of 1.0 gm. daily, but the exact amount absorbed during the 1st few days is uncertain because of vomiting. From the 1st postoperative day until death 40 days later, the patient remained in a hyponatremic state that did not re-

spond to a diet containing 2.0 gm. of sodium combined with added sodium chloride intermittently (Fig. 3).

On the 6th postoperative day an electrocardiogram indicated right-bundle-branch block. One taken 12 days later showed a reversion to the previous pattern.

She remained weak and intermittently drowsy. Repeated physical examinations revealed no petechiae and no splenomegaly. On the 42d hospital day she was febrile in the evening, and a repeat examination, including a search for petechiae and splenomegaly, was unrewarding. A pericardial friction rub was heard for the 1st time. It was thought that this probably represented a recrudescence of active rheumatic fever, and 3.6 gm. of aspirin a day was started. Two blood cultures were drawn and were negative. Symptoms of salicylism developed 5 days later, and aspirin was discontinued for 1 day and then reinstituted at the lower dosage of 2.4 gm. a day.

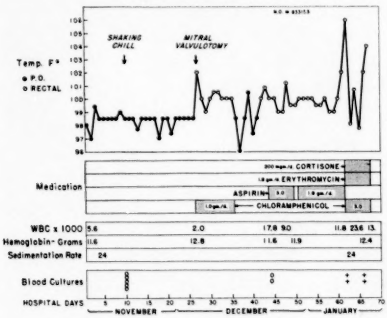

FIGURE 3. *Clinical Course in Case 2.*

On the 52d hospital day she had a sudden gain in weight of 2.3 kg. (5 pounds). Massive edema of the lower part of the legs developed, with burning pain in both feet; 2 cc. of Thiomerin on 3 successive days failed to clear the edema.

On the evening of the 61st hospital day she had a sudden spell of weakness and apprehension and began to cough up frothy sputum. This attack subsided rapidly after the administration of Demerol. Physical examination at that time showed no petechiae and no splenomegaly. The frothy sputum later grew out an alpha-hemolytic streptococcus and *Staph. aureus*. Early the next morning the temperature began to rise and she became cold and cyanotic. By that afternoon the temperature had reached 106°F. Blood cultures were drawn, and chloramphenicol, 3.0 gm. a day, was begun empirically in combination with erythromycin, 1.8 gm. a day. The patient was known to be sensitive to penicillin. Owing to a high serum potassium of 8.7 milliequiv. per liter, as well as the severe shocklike state, Cortisone, 200 mg. a day, was also begun.

On the following day she looked better. The temperature dropped precipitously to normal, and the serum potassium fell to 4.9 milliequiv. per liter. However, she soon relapsed to a markedly dyspneic and stuporous state. By the 63d hospital day blood cultures had grown out coagulase-positive *Staph. aureus*. The blood pressure remained low in a range of 70/40 to 80/60. On the 67th hospital day she had several short bouts of syncope, and during 1 of these the pulse was noted to fall from 120 to 60. The pulse gradually returned to 120, and with it a state of consciousness returned. She remained drowsy, but was able to be aroused. That evening, the temperature rose to 103°F., the respirations became gasping, cyanosis deepened, and she was found dead in bed later that night.

At autopsy the pericardial cavity was obliterated by fibrous and fibrinous adhesions. The heart was enlarged, weighing 470 gm. Both atria were hypertrophied and dilated. The right ventricle showed hypertrophy. Grossly, the myocardium was unremarkable except for the posterior portion of the interventricular septum, which had a blotchy, yellowish discoloration. No mural thrombi were present. The mitral valve was stiff and markedly calcified, and the chordae tendineae were shortened, thickened and fused. The valve opening measured 2.5 cm. in length, of which 1 cm. represented the fracture at the anterior commissure and 0.8 cm. represented the posterior fracture. The anterior fracture appeared clean. Posteriorly, the fracture extended into a large calcified nodule measuring 2.5 cm. by 1.5 cm. by 1 cm. (Fig. 4). The terminal 3 or 4 mm. of the fracture line communicated with a hematoma within the nodule. In this region there was soft, brown amorphous material in which numerous gram-positive cocci in clusters were demonstrated by direct smear. Cultures showed an abundant growth of *Staph. aureus*. Microscopical sections through this area in the same plane as the fracture line showed a great deal of calcification surrounded by areas of fibrous tissue, with numerous macrophages, lymphocytes and polymorphonuclear leukocytes, as well as many capillaries. A large area of hemorrhage was present. Clusters of gram-positive cocci were seen throughout the central calcified area. The inflammatory reaction extended to the base of the mitral valve but not into the myocardium in this region. There was no bacterial growth at the anterior commissure. There was minimal scarring of both the aortic and tricuspid valves. Numerous microscopical sections through the heart muscle revealed multiple focal abscesses, with numerous polymorphonuclear leukocytes and gram-positive cocci. These were especially numerous in the posterior interventricular septum, where the yellowish discoloration was seen grossly. No Aschoff nodules were found. The lungs were edematous, with many areas of emphysema. Slight intimal

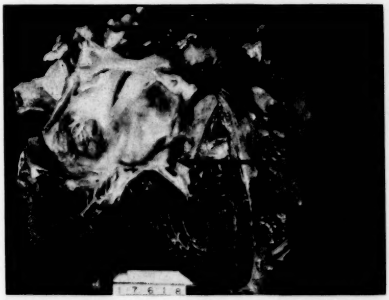

FIGURE 4. *Gross Appearance of the Heart in Case 2, Showing the Site of the Posterior Fracture Extending into a Calcified Nodule with a Central Hematoma.*

hyalinization of the larger pulmonary arteries and numerous hemosiderin-filled macrophages were noted. The liver, which weighed 2040 gm., showed central congestion and fibrosis. The spleen weighed 540 gm. The remaining organs were grossly unremarkable, but on microscopical sections focal acute staphylococcal abscesses, similar to those found in the myocardium, were seen in the brain, spleen and kidneys and in 1 adrenal gland.

CASE 3. A.L. (M.G.H. 859583), a 42-year-old housewife, was admitted to the Massachusetts General Hospital for mitral valvulotomy on November 29, 1954. There was no past history of rheumatic fever. At the age of 22, she was informed of a heart murmur during a routine physical examination. The first symptoms were noted in 1943 during the last 4 months of her 5th pregnancy, when dyspnea and rapid heart action were experienced. Delivery was accomplished without difficulty, however, and she did well for the next 3 years except for dyspnea on marked exertion. In 1949 she consulted her physician because of dyspnea, precordial pain and weakness. On restricted activity and a

low-salt diet, her symptoms were well controlled until January, 1951, when she began to have a low-grade fever, increasing weakness and tachycardia. Although no positive blood cultures were obtained, subacute bacterial endocarditis was suspected, and therefore 2,700,000 units of procaine penicillin a day was given for 17 days, after which she became afebrile. Over the next 3 years there were 3 attacks of pulmonary edema, with coughing of pink, frothy sputum during the last attack. Because of the bouts of pulmonary edema and increasing dyspnea on exertion, mitral valvulotomy was considered indicated.

On physical examination, at the time of admission, there was no evidence of congestive heart failure. The heart was not enlarged. The pulmonic 2d sound was increased and louder than the aortic. The mitral 1st sound was increased, and there was an opening snap. A Grade 4 diastolic rumble was noted at the apex. No systolic murmurs were heard. A mitral valvulotomy was performed on December 3. The atrial appendage was of normal size and contained no clots. The mitral valve would not admit a finger tip. It was not calcified. The valve split well and no regurgitation was noted after operation. The patient was given 200,000 units of penicillin every 8 hours for a week beginning on the day of operation. The temperature was 101°F. (by rectum) on the 1st postoperative day but fell to normal within the next 3 days, and the postoperative course was entirely uneventful.

The patient was greatly improved after the valvulotomy and was doing well until about 2 weeks before her last hospitalization on April 4, 1955. At that time, she began to feel unwell generally. There were generalized joint pains, and painful, swollen, red spots on the fingers and toes were noted. The temperature ranged around 99°F. by mouth.

On the day before her last admission she suddenly had a shaking chill followed by elevation in temperature to 104°F. Shaking chills continued, and a slight sore throat was noted. She was admitted to the Exeter Hospital, Exeter, New Hampshire, on April 4, 1955.*

On physical examination she appeared acutely ill and dyspneic. The heart was slightly enlarged to percussion. An apical diastolic rumble was heard, but no systolic murmurs were noted. A few petechiae were found. The spleen was not felt. There were inspiratory rales at both lung bases. Blood cultures were drawn, and 600,000 units of procaine penicillin every 12 hours was started. On April 21 the blood culture taken on admission grew out a *Staph. aureus* that was resistant to penicillin and sensitive to chlortetracycline, chloramphenicol, bacitracin, tetracycline, oxytetracycline and erythromycin. The antibiotics administered are noted in Figure 5. Despite a steady decline in temperature, the course was generally unfavorable. Because of the general deterioration and a drop in blood pressure, cortisone was started on April 23, with a return of the blood pressure to more normal levels. New petechiae appeared daily, and there was increasing left-upper-quadrant pain. Urinary output became progressively less, and the patient became disoriented, with increasing dyspnea.

She died on April 30. Permission for autopsy was not obtained.

Discussion

Bacterial endocarditis after cardiac surgery is not a common complication. In two large series, with a total of 600 cases, no case was reported.[9,10] The 3 patients described above are from a group of over 150 patients undergoing mitral valvulotomy at the Massachusetts General Hospital since 1951. The increasing hazard of postoperative infections with antibiotic-resistant staphylococci has been repeatedly documented.[11] Two of the 3 patients received penicillin during the immediate postoperative period, and in all the staphylococcus recovered was penicillin resistant.

The autopsy findings in Case 1 deserve special attention. The fenestration in the aortic valve was thought to represent the site of a previous bacterial infection. Subacute bacterial endocarditis involving this area could well be the explanation for the febrile episode occurring in the spring of 1954, nine months before death. It is of interest that Case 3 also had had an earlier undiagnosed febrile illness, which may have been bacterial endocarditis.

The staphylococcus was the only organism cultured from the blood in Case 1 during life. This organism was repeatedly cultured both at the onset of the illness and at the time of the exacerbation after therapy had been discontinued. Despite the fact that *Str. viridans* was cultured from the vegetation on the

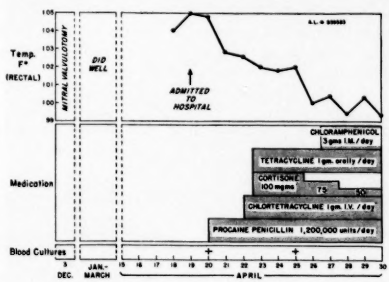

FIGURE 5. *Clinical Course in Case 3.*

heart valve at autopsy, there seems little doubt that the *Staph. aureus* was the major offending organism.

The clinical picture in cases previously reported, as well as in the 3 reported above, has been variable, and no well defined clinical syndrome has been observed. The onset has varied from two days postoperatively to as long as three months after surgery. However, attention should be called to some of the clinical features that may be peculiar to staphylococcal endocarditis observed in these patients. Staphylococcal endocarditis is usually regarded as an acute febrile illness heralded by a sudden onset of chills and fever. However, there may be a subacute period of nonspecific symptoms and low-grade fever. This was present in 2 of the 3 patients, and has been previously observed by Thayer[12] and by Fisher et al.[13] The awareness of this undramatic period preceding the onset of frank chills and fever and lasting sometimes as long as two or three weeks is an important clue to earlier recognition of staphylococcal endocarditis. The absence of petechiae and of a palpable spleen has been previously noted in staphylococcal endocarditis.[6] In this series, Case 3, who had showers of petechiae in the early course of her illness, was the only 1 who had either of these features. The absence of petechiae and of splenomegaly, therefore, does not help exclude the possibility of this diagnosis.

An important complication in the postoperative period to be differentiated from bacterial endocarditis

*We are indebted to Dr. Charles S. Houston, of the Exeter Clinic, Exeter, New Hampshire, for furnishing data on this patient.

is the reactivation of rheumatic fever — the so-called "postvalvulotomy syndrome." At the onset, there are several features common to both. The tendency of staphylococci to form focal collections of pus makes early recognition and treatment of particular importance. In any postvalvulotomy patient presenting vague symptoms and fever, bacterial endocarditis must be included in the differential diagnosis.

Summary

Three cases of bacterial endocarditis after mitral-valve surgery are presented. These represent the only cases of bacterial endocarditis occurring in over 150 patients who have had mitral valvulotomies at this hospital. In all 3 the offending organism was a penicillin-resistant *Staphylococcus aureus* (in sharp contrast to the usual causative organism in bacterial endocarditis — *Streptococcus viridans*).

References

1. Roantree, R. J., and Rantz, L. A. Fatal staphylococcal endocarditis treated with erythromycin: rapid development of resistance in vivo and in vitro. *Arch. Int. Med.* **95**:320-325, 1955.
2. Likoff, W., Berkowitz, D., Denton, C., Goldberg, H., and Reale, A. Transventricular commissurotomy in aortic stenosis: clinical evaluation. *J.A.M.A.* **157**:1367-1373, 1955.
3. Panting, N., Epstein, M. A., and Bolomey, A. A. Acute bacterial endocarditis following mitral valvuloplasty. *Am. Heart J.* **49**:455-458, 1955.
4. Brunsdon, D. F., Enticknap, J. B., and Milstein, B. B. Case of subacute bacterial endocarditis due to Pseudomonas pyocyanea complicating valvotomy for advanced mitral stenosis. *Guy's Hosp. Rep.* **102**:303-312, 1953.
5. Stapleton, J., Harvey, W. P., and Hufnagel, C. Probable acute bacterial endocarditis following valve surgery. *Bull., Georgetown Univ. M. Center* **6**:5-7, 1952.
6. Dowling, H. F., Lepper, M., Caldwell, E. R., and Spies, H. W. Staphylococcic endocarditis: analysis of 25 cases treated with antibiotics, together with review of recent literature. *Medicine* **31**: 155-176, 1952.
7. Libman, E., and Friedberg, C. K. *Subacute Bacterial Endocarditis.* (Reprinted from *Oxford Loose-Leaf Medicine.*) Edited by H. A. Christian. 108 pp. New York: Oxford, 1941.
8. Genkins, G., Uhr, J. W., and Bryer, M. S. Bacitracin nephropathy: report of case of acute renal failure and death. *J.A.M.A.* **155**:894-897, 1954.
9. Ellis, L. B., and Harken, D. E. Clinical results in first five hundred patients with mitral stenosis undergoing valvuloplasty. *Circulation* **11**:637-646, 1955.
10. Janton, O. H., Glover, R. P., O'Neill, T. J. E., Gregory, J. E., and Froio, G. F. Results of surgical treatment for mitral stenosis: analysis of one hundred consecutive cases. *Circulation* **6**:321-333, 1952.
11. Howe, C. W. Postoperative wound infections due to *Staphylococcus aureus*. *New Eng. J. Med.* **251**:411-417, 1954.
12. Thayer, W. S. Studies on bacterial (infective) endocarditis. *Johns Hopkins Hosp. Rep.* **22**:1-185, 1926.
13. Fisher, A. M., Wagner, H. N., Jr., and Ross, R. S. Staphylococcal endocarditis. *Arch. Int. Med.* **95**:427-437, 1955.

LABORATORY-ACQUIRED HISTOPLASMOSIS*

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BALTIMORE

ALTHOUGH naturally acquired histoplasmosis is being recognized with increasing frequency[1] there are few reports in the literature of infection with *Histoplasma capsulatum* acquired in the laboratory. Sulkin and Pike,[2] in 1951, summarized 1342 cases of infections presumably acquired as the result of laboratory work in the United States. Approximately a third of these infections have been recorded in the literature; the remainder were discovered by means of a questionnaire mailed to nearly 5000 laboratories. Thirty-nine of these patients died — a mortality of 3 per cent. No cases of histoplasmosis were recorded in this survey.

In 1952 Furcolow et al.[3] described conversion of the histoplasmin skin test in 17 laboratory personnel employed at the Mycoses Laboratory of the Public Health Service in Kansas City, Kansas. Seven of these 17 patients gave histories of definite illnesses of an influenzal nature occurring about the time the skin tests changed from negative to positive. Five of this group had suggestive findings on x-ray study of the chest at the time of their illness and skin-test conversion.

In 1953, Nilzén and Paldrok[4] reported 7 cases from a laboratory in Stockholm where work was being done with *H. capsulatum*. These patients had positive histoplasmin skin tests and respiratory symptoms, accompanied in some cases by pulmonary infiltrates on roentgenograms of the chest. *H. capsulatum* was not recovered from the sputum, gastric washings and bronchial secretions. However, since positive histoplasmin skin tests are rare in Sweden, the authors believed that the patients had histoplasmosis.

Since there are so few reports of laboratory-acquired histoplasmosis in the literature we believe that it is important to describe 3 patients with this disease recently seen.

Case Reports

Case 1. M.G., a 39-year-old female laboratory technician, was admitted to the hospital on March 15, 1949, complaining of fever, general malaise and a slight nonproductive cough for 3 weeks. Three days before admission she had a chill with a temperature elevation to 102°F. The fever persisted up until the time of hospitalization.

From October, 1948, until the time of admission, she had worked on a series of *H. capsulatum* cultures from a man who was hospitalized for histoplasmosis.¶

In 1943, the patient had had a radical mastectomy for a carcinoma of the right breast, and in 1947 a fenestration operation was done on the right ear.

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¶This case was reported by Rodger and his associates.[5]

Physical examination was negative except for an elevated temperature, absence of the right breast, and the changes following the fenestration operation.

The white-cell count was 4950, with a normal differential. The corrected sedimentation rate was 38 mm. per hour (Wintrobe method). Typhoid and paratyphoid agglutinations were positive in low titers, but the patient had recently been immunized against typhoid and paratyphoid. Other laboratory studies were within normal limits. No studies for histoplasmosis were done.

The patient was treated symptomatically. She continued to have a low-grade fever until the last week in the hospital. She gradually improved and was discharged after a hospital stay of 22 days.

She continued to have fatigue and noted a gradual weight loss. She was rehospitalized from May 24 to June 25, 1949. The findings on physical examination were unchanged. Laboratory studies again showed no significant changes except for a +++ cephalin-cholesterol flocculation in 48 hours, a thymol turbidity of 14 units and zinc sulfate flocculation of 16 units. Roentgenogram of the chest, which had been normal on January 18 (Fig. 1) and on the previous admission now showed changes at the right base (Fig. 2).

The patient again had a low-grade fever and was treated with chlortetracycline. Again, no diagnosis was established.

The 3d hospital admission was in March, 1950, for fever of undetermined origin. Again, liver-function tests were positive, and the changes on the film of the chest were still present.

The patient was then followed again in the Outpatient Department. The liver-function tests remained positive. The

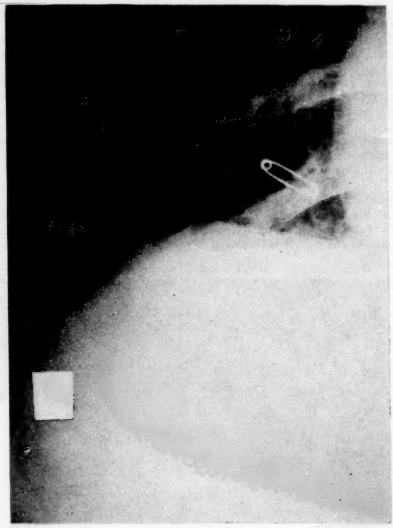

FIGURE 1. *Enlargement of the Right-Lower-Lung Field in a Roentgenogram in Case 1, Taken before Onset of the Illness.*

changes in the right lower lung seemed to resolve, leaving a nodule that remained stable until a roentgenogram of the chest taken on March 18, 1954 (Fig. 3), showed apparent enlargement of the nodule and a thoracotomy was advised. Preoperatively, the liver-function tests were negative. A skin test with purified-protein derivative of tuberculin, 0.00002 mg., was positive.

At operation a nodule about 1.5 by 1 by 1.5 cm. was removed from the right lower lobe. On frozen section no evidence of neoplasm was found; accordingly, no further resection was done.

The lesion was definitely granulomatous on further study. Because of small spherical bodies present in the sections, a pathologist thought that the etiologic agent was *H. capsulatum*. At another laboratory the spherical bodies were not considered to be *H. capsulatum*, but because of the appearance of the lesion, histoplasmosis was thought not to be ruled out. Cultures and guinea-pig inoculations of the material were not successful in demonstration of an etiologic agent.

After the operation on the patient a skin test with 0.1 ml. of 1:1000 histoplasmin was strongly positive, with a

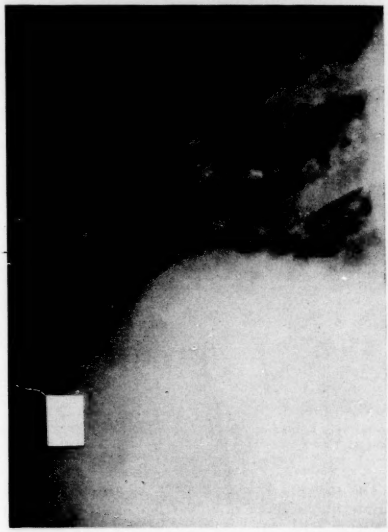

FIGURE 2. *Enlargement of the Area Presented in Figure 1, Showing a Pulmonary Infiltrate That Developed after the Onset of the Illness.*

20 mm. area of edema in 48 hours. The patient had previously had a negative histoplasmin skin test in July, 1948. Complement-fixation tests for histoplasmosis were negative.

Convalescence was slow. Treatment with streptomycin and para-aminosalicylic acid was given for 3 months until the results of the cultures were known. Thirteen months later there was no evidence of dissemination of the disease.

Although proof of the etiology of the lesion in this case was not obtained by culture, we believe that the illness was caused by *H. capsulatum*. It may be difficult or impossible to culture the organism from old granulomatous pulmonary lesions of histoplasmosis. Zimmerman[6] was able to stain the organisms in granulomas removed from 19 patients. In many cases cultures of these lesions had been negative. Puckett,[7] in 22 cases of pulmonary histoplasmosis, succeeded in culturing *H. capsulatum* in only 1 case but demonstrated the organisms histologically in all the lesions; he believed that the organisms in the lesions of the healed or healing stage are probably not viable.

Forsee and his associates[8] were able to culture *H. capsulatum* from only 1 of 30 resected pulmonary lesions in which the organisms had been demonstrated histologically.

FIGURE 3. *Tomogram of the Right-Lower-Lung Field in Case 1, Taken Shortly before Operation, Showing the Circumscribed Residual Lesion.*

The patient's febrile course with a pulmonary infiltrate at the onset of illness is consistent with the clinical picture of histoplasmosis, and residual lesions may remain after the acute phase of the illness is past.[1] Furthermore, conversion of the histoplasmin skin test is additional evidence for the diagnosis of histoplasmosis.

CASE 2. E.C.P., a 36-year-old physician, was injecting the heart valves of a dog with the yeast-phase culture of *H. capsulatum* when some of the material sprayed on his forehead. One week later, while he was injecting the valves of another dog with the same culture, material was sprayed into his right conjunctival sac. Six days after the 2d episode, he noted soreness in the cervical region just below the angle of the mandible. Four days later, there was soreness of the eye and edema of the palpebral conjunctiva and upper lid.

The past history was irrelevant except for infectious hepatitis when the patient was 14 and a positive tuberculin test when he was in medical school.

General physical examination showed no other abnormalities except absence of the left testis, which had been removed 7 years previously because of a seminoma. There were marked edema and redness of the right upper eyelid and less edema of the right lower eyelid, most severe temporally (Fig. 4). The superior tarsal conjunctiva was edematous and congested, with induration and tenderness about the accessory lacrimal gland. The bulbar conjunctiva and inferior tarsal conjunctiva were mildly congested. A foreign-body sensation was present under the upper lid, and lacrimation was profuse. Preauricular and upper anterior cervical lymph nodes were painful, tender and enlarged. Pupillary reactions were normal. Corrected visual acuity was 20/15 in each eye, and no intraocular abnormality was noted by biomicroscopical or funduscopic examination.

X-ray study of the chest was negative. Smears from the upper conjunctival fornix and about the lacrimal-gland duct showed no organisms. Scrapings from the most involved area of the right upper conjunctival fornix yielded a few epithelial cells and occasional gram-positive cocci. Cultures taken from the lower lid and the upper and lower conjunctival fornices all grew hemolytic *Staphylococcus albus* but no colonies of *H. capsulatum*. On admission a histoplasmin skin test was negative, but another test 10 days later showed a 35-mm. area of erythema with a 15-mm. indurated and edematous center. Complement fixation for histoplasmosis was negative. The toxoplasmosis dye test was positive in a dilution of 1:64, but when the patient was first seen the complement fixation was negative. An agglutination test for brucella was positive in a dilution of 1:40, and that for tularemia was positive in a dilution of 1:20. Hematologic examination, consisting of white-cell count and differential counts, hemoglobin, hematocrit and sedimentation rate, was negative, as was a urinalysis.

The patient was given 5 per cent sodium propionate ophthalmic drops in each eye 6 times daily.

FIGURE 4. *Photographs of the Eye in Case 2 when the Patient Was First Seen* (A) *and of the Upper Tarsal Conjunctiva Taken Three Days Later* (B).

Small hemorrhagic areas were seen along the temporosuperior margin of the right tarsal plate 3 days after admission, giving way to lymph-follicle hyperplasia during the next week (Fig. 4*B*). Thirteen days after the patient was first seen a tiny, shallow ulcer, with a whitish, indolent surface and sloping sides and surrounded by lymph follicles, could be seen over the upper border of the tarsal plate. The ulcer healed during the next 5 days, and lymph follicles were reduced in number. The lid swelling and congestion were greatly diminished at this time. Three days later no appreciable change could be noted. Repeat complement fixation for histoplasmosis, as well as hematologic and urine examinations, was negative.

The patient went home and continued the sodium propionate drops for 3 more weeks. Two weeks after cessation of the drops he returned to the clinic with no complaints. The only remaining evidences of the infection were some residual lymph follicles on the upper tarsal plate and slightly enlarged, nontender preauricular and anterior cervical lymph nodes. X-ray study of the chest was negative, and hematologic and urine findings were normal 24 days after the onset. An agglutination test for tularemia 4 months after the onset was negative. The patient was asymptomatic 1 year after the onset of his illness.

A culture of *H. capsulatum* similar to that splashed into the patient's eye was tested by Dr. Chester W. Emmons, of the National Microbiological Institute, for sensitivity to ascosin and to the sodium propionate drops. The sodium propionate drops gave a larger area of inhibition of growth than the ascosin solution used. The latter substance has been found effective in the treatment of experimental histoplasmosis in mice.[9]

Although *Histoplasma capsulatum* could not be cultured from this patient's conjunctiva, he undoubtedly had histoplasmosis because of his exposure and because of the conversion of the histoplasmin skin test. Lymph-node and conjunctival biopsy and scraping of the conjunctival ulcer for cultures were not done because of the danger of dissemination of the infection by these procedures. A search of the literature fails to reveal any similar case of histoplasmosis although Reid and his associates[10] and Krause and Hopkins[11] have described lesions of the fundus of the eye presumably caused by *H. capsulatum*.

CASE 3. A.H., a 45-year-old sanitary engineer, had 11 teeth extracted on May 8, 1953. On the following day the temperature was elevated to 101°F. He was given penicillin over the next 3 days, after which he was afebrile. On June 21 his remaining teeth were extracted, after which the temperature was 103°F. Again, he was given penicillin but remained febrile. On June 29, an X-ray study of the chest did not show any lesions; a leukocytosis was found. He was then given 1.0 gm. of chlortetracycline daily for 7 days, but this medication was discontinued because nausea and a black tongue developed. He had no further symptoms until August 19, when he began to have generalized aching and fever. The administration of 1.0 gm. of chlortetracycline had no effect on the symptoms or the fever. He was then admitted to another hospital, where, on chest roentgenogram, an infiltrate in the right upper lung, with a suggestion of cavitation, was found. No acid-fast organisms were observed on smear. Skin tests with purified-protein derivative of tuberculin in a dose as high as 0.005 mg. were negative. A skin test with histoplasmin was positive.

This patient worked at the Environmental Health Center of the United States Public Health Service in Cincinnati, Ohio. Although he did not work with *H. capsulatum*, his office was on the floor below a laboratory where histoplasmosis research was being done. On several occasions, he had been in a classroom on the same floor as this laboratory, which had a common ventilation system with the classroom.

On September 13, he was transferred to this hospital with a tentative diagnosis of histoplasmosis.

Physical examination showed signs of consolidation at the apex of the right lung, but was otherwise within normal limits.

The white-cell count ranged between 9900 and 12,200, with a slight shift to the left. The hemoglobin was 13 gm., and the sedimentation rate was 31 mm. per hour (Wintrobe method). Three concentrated sputum specimens showed no acid-fast organisms on smear. Sputum and blood cultures yielded neither fungi nor bacteria on culture. The complement fixation for histoplasmosis was reported positive in a dilution of 1:16 at 1 laboratory and 2 weeks later was again reported positive in a dilution of 1:32. However, another laboratory found this test to be negative. A skin

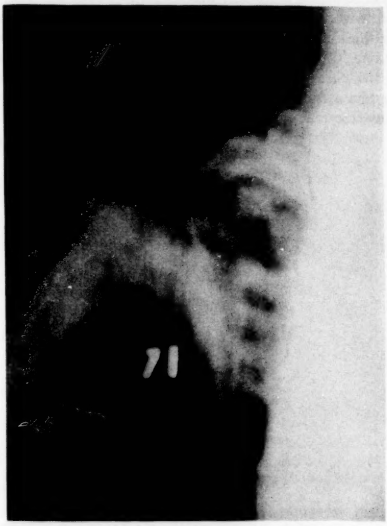

FIGURE 5. *Tomogram of the Right Upper Lung in Case 3.*

test with histoplasmin was positive in a dilution of 1:1000, and 0.005 mg. of purified-protein derivative of tuberculin gave a positive reaction; lower concentrations of tuberculin gave negative reactions on skin test. A roentgenogram of the chest showed an infiltrate at the apex of the right lung, with several radiolucent areas suggestive of cavitation (Fig. 5).

During the 1st 2 weeks in the hospital the patient was afebrile and felt fairly well. Bronchoscopy yielded no findings of significance. A tentative diagnosis of pyogenic lung abscess was made, and treatment with a combination of penicillin, streptomycin and sulfisoxazole was begun on September 29. In spite of treatment, 5 days later the temperature spiked to 102°F. On continued treatment, however, it fell gradually to normal again.

It was decided that thoracotomy should be done because the roentgenogram of the chest, which initially had shown improvement in the lesion in the upper lobe, later indicated progression of the lesion. On November 4, the right upper lobe was resected. The apex was scarred and was firm. A number of cystic areas or abscesses were found. Sections of the lobe showed many abscess cavities with surrounding inflammation and fibrosis. At 1 laboratory periodic acid stain for fungi was thought to show *H. capsulatum* but pathologists at another institution believed that the apparent organisms were artifacts. However, the lung tissue was injected into the peritoneum of a guinea pig, and 20 days later the lung, liver, spleen and peritoneal tissues of the

guinea pig were cultured on Sabouraud's agar. The culture showed *H. capsulatum*, which was confirmed by Dr. C. W. Emmons, of the National Microbiological Institute.

After operation complete paralysis of the right upper extremity developed but gradually improved. Five months later the patient felt well and had completely recovered from the paralysis of the brachial plexus. There was almost complete expansion of the right lung. When last heard from 7 months after operation, he was completely asymptomatic.

Since this patient lived in an area where histoplasmosis is endemic, it is possible that he acquired his disease in some way besides a laboratory infection. However, he undoubtedly was exposed to organisms in the building where he worked. This case also illustrates the difficulty in diagnosis of histoplasmosis. Such cases of pulmonary histoplasmosis with acute systemic symptoms are being described with increasing frequency in the literature.[1]

Summary and Conclusions

Two cases of probable and 1 of definite histoplasmosis acquired in the laboratory are reported.

With increasing recognition of histoplasmosis and exposure of technical and professional personnel to organisms cultured from patients with the disease it is likely that histoplasmosis will be acquired with increasing frequency in the laboratory.

References

1. Schwartz, B. Histoplasmosis of lungs. *Arch. Int. Med.* **94**:970-994, 1954.
2. Sulkin, S. E., and Pike, R. M. Survey of laboratory acquired infections. *Am. J. Pub. Health* **41**:769-781, 1951.
3. Furcolow, M. L., Guntheroth, W. G., and Willis, M. J. Frequency of laboratory infections with Histoplasma capsulatum: their clinical and x-ray characteristics. *J. Lab. & Clin. Med.* **40**:182-187, 1952.
4. Nilzén, A., and Paldrok, H. Laboratory infection caused by Histoplasma capsulatum. *Acta dermat.-venereol.* **33**:329-341, 1953.
5. Rodger, R. C., Terry, L. L., and Binford, C. H. Histoplasmosis, cryptococcosis and tuberculosis complicating Hodgkin's disease. *Am. J. Clin. Path.* **21**:153-157, 1951.
6. Zimmerman, L. E. Demonstration of histoplasma and coccidioides in so-called tuberculomas of lung. *Arch. Int. Med.* **94**:690-699, 1954.
7. Puckett, T. F. Pulmonary histoplasmosis: study of twenty-two cases with identification of H. capsulatum in resected lesions. *Am. Rev. Tuberc.* **67**:453-476, 1953.
8. Forsee, J. H., Puckett, T. F., and Hagman, F. E. Surgical considerations in localized pulmonary histoplasmosis. *J. Thoracic Surg.* **26**:131-139, 1953.
9. Emmons, C. W., and Haberman, R. T. Ascosin in treatment of experimental histoplasmosis in mice. *Antibiotics & Chemother.* **3**:1204-1210, 1953.
10. Reid, J. D., Scherer, J. H., Herbut, P. A., and Irving, H. Systemic histoplasmosis: systemic histoplasmosis diagnosed before death and produced experimentally in guinea pigs. *J. Lab. & Clin. Med.* **27**:419-434, 1942.
11. Krause, A. C., and Hopkins, W. G. Ocular manifestation of histoplasmosis. *Am. J. Ophth.* **34**:564-566, 1951.

MEDICAL PROGRESS

VALUE OF CULDOSCOPY IN GYNECOLOGIC DIAGNOSIS*

Report of 150 Cases

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BOSTON

In July, 1953, a program to employ culdoscopy to the fullest extent of its usefulness in the diagnosis of pelvic disease was embarked upon at the Vincent Memorial Hospital. It was hoped in this manner to settle to the satisfaction of those participating the question of the value, ease of application and limitations of the procedure, as well as to add an important method to the diagnostic armamentarium of the Gynecological Service.

No "routine" culdoscopies were carried out in an effort to accumulate large numbers of cases. Culdoscopy was done only when a specific indication for its application existed and circumstances were such that actual visualization of the pelvic viscera was deemed essential to the solution of a clinical problem.

In the ensuing two years, 150 culdoscopies have been performed for a variety of indications. This experience has firmly convinced those who took part in the program of the great value of this procedure in facilitating the diagnosis of a number of gynecologic disorders. Information obtained in this manner frequently not only provides the clue to proper medical or surgical therapy but also makes it possible to avoid laparotomy for diagnosis only.

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Technic

Albert Decker performed the first culdoscopy in 1942, and to him belongs the credit for perceiving and finally proving that the knee-chest position would make possible the use of a modern endoscopic instrument through the vaginal route to obtain a superior view of the pelvic viscera.[1] The procedure has since been employed in many clinics throughout the world, and reports of its use have in general been favorable and enthusiastic.[2-6]

A detailed description of the instrument he designed and his personal technic is contained in a recent monograph by Decker[7] and will not be attempted here. However, it should be emphasized that as with any diagnostic tool, success in its use lies in keeping it simple and readily available. Happily, culdoscopy lends itself well to a simple technic. As a result its use will often be elected in borderline clinical

situations in which visualization of the pelvic organs may not seem absolutely necessary or even on first thought likely to be profitable, as well as in situations such as suspected ectopic pregnancy in which laparotomy would often be mandatory if there were not some other means of visualizing the pelvis.

Preparation of the Patient

All patients have been admitted to the hospital for the procedure, and all culdoscopies have been done in the operating room. It has not seemed feasible or desirable to do them in the clinic on an outpatient basis, although this is done to some extent in a few centers and one author reports the use of the culdoscope in his office practice.[8] The perineum and vulva are shaved, and unless the procedure is to be done as an emergency, an enema is administered. Premedication consists of the customary light barbiturate sedation along with Demerol and scopolamine in the usual doses. It has been found helpful to send the patient to the operating room with a urethral catheter already in the bladder. This is drained and removed just before she is placed on the operating table, for catheterization of the bladder with the patient in the knee-chest position frequently results in a large "pneumobladder," which may interfere with easy visualization of all aspects of the pelvic organs. Preliminary catheter placement eliminates the cumbersome position changes and table adjustments that would otherwise be necessary in the operating room.

It is also helpful to explain in some detail to the patient beforehand the purpose of the procedure and the reason why it will be done in the knee-chest position. The knowledge that a laparotomy may be avoided as a result of information obtained by culdoscopy, or that an actual view of the pelvic organs (which may be the only way in which a puzzling problem can be solved) can be had simply and easily by this method is readily appreciated by all patients. Explanation and reassurance along these lines have helped avoid apprehension later in the operating room and has tended to put more at ease the few who might be embarrassed by the position.

Positioning of the Patient

As conceived and emphasized by Decker[1] the knee-chest position is indispensable. The patient can be helped to maintain this position with relative ease and comfort without any special or complicated apparatus. Figure 1 shows how a standard operating table can be quickly adjusted for this purpose. On this service no patients who could not comfortably tolerate or maintain the knee-chest position for the time necessary to carry out the procedure have been encountered.

Palmer[9] reports a combination of steep Trendelenburg and lithotomy positions, which would allow the use of a general anesthetic and which, he states, permits a satisfactory view of the pelvis. This service has had little experience with this method since local anesthesia has been perfectly satisfactory in the cases under discussion. Because the negative-pressure effect created in the pelvis is much greater in the knee-chest position, it seems likely that cul-de-sac puncture will be easier and safer and the view obtained usually superior in this position.

However, the combined exaggerated Trendelenburg and lithotomy position was employed for culdoscopy in 8 patients already under Pentothal anesthesia. In 3 cases provisional palpation of a previously undetected adnexal mass while the patients were under anesthesia for a diagnostic dilatation and curettage

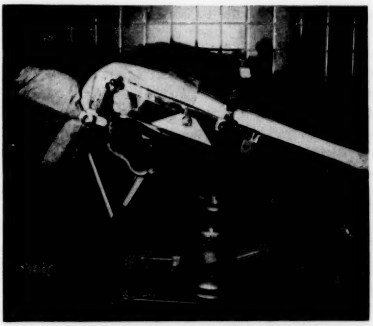

FIGURE 1. *Standard Operating-Room Table Adjusted for Use of the Knee-Chest Position during Culdoscopy.*

prompted culdoscopy. One examination was negative, the others revealing Stein–Leventhal ovaries and a pedunculated fibroid respectively. Five patients were undergoing curettage because of abnormal bleeding assumed preoperatively to be due to early incomplete abortions. Because of failure to obtain retained decidual tissue in spite of a history consistent with early pregnancy, culdoscopy was deemed advisable to rule out possible ectopic pregnancy. In 3 cases culdoscopic examination was negative, and the final diagnosis was metropathia, a period of amenorrhea having been followed by excessive functional bleeding. Unsuspected pelvic inflammatory disease was discovered in the remaining 2 patients.

Thus, though the knee-chest position is the preferred one, a satisfactory view can often be obtained in lithotomy position. This knowledge may prove of particular value when the patient is already under anesthesia before the desirability of culdoscopic examination becomes apparent. It should be mentioned that when a dilatation and curettage is being done simultaneously, placing a dilator in the cervical canal to manipulate the uterus is a most helpful maneuver during culdoscopy in the lithotomy position.

Anesthesia

Local infiltration anesthesia is the procedure of choice and was employed in all but a few of these cases. The area in the posterior cul-de-sac through which puncture is made is relatively insensitive, and it is only necessary to inject 1 or 2 cc. of 1 per cent procaine directly into the vaginal mucosa at this point. Care must be taken not to deposit procaine in any significant amount between the vaginal mucosa and the underlying peritoneum, lest the peritoneum be elevated away and its penetration by the trocar made difficult. Nearly all patients experience a momentary uncomfortable sense of pressure as the trocar is introduced, but the remainder of the procedure is rendered quite painless by local anesthesia alone, even in the presence of sensitive inflammatory conditions in the pelvis.

To date the only indication for anything but local anesthesia has been the necessity for dilatation of an intact hymen before culdoscopy, and a low spinal anesthetic has proved very satisfactory. Padded uprights attached to the sides of the table to which the thighs are strapped are all that is necessary to help the patient maintain the position when spinal anesthesia is employed.

Instruments

Only the minimum of equipment is necessary in addition to the Decker culdoscope with accompanying trocar and cannula. A Sims speculum, cervical tenaculum and an ordinary battery box, such as is employed with a cystoscope, are the only essential items. Included with the culdoscope is a cervical cannula and a set of graduated tips through which methylene blue dye may be instilled into the uterus to test for tubal patency. The culdoscope itself should not be autoclaved or exposed to alcoholic solutions but is easily sterilized by immersion in an aqueous solution of Zephiran for an hour before use. It is usually necessary to warm the lens sufficiently to prevent fogging during observation within the peritoneal cavity, and a basin of hot saline solution should be available for this purpose.

Cul-de-Sac Puncture

After preparation of the vulva and vagina with a nonirritating antiseptic such as aqueous Zephiran solution, a single laparotomy drape sheet is placed over the field so as to permit simultaneous abdominal palpation. A lubricated Sims speculum is introduced into the vagina. Elevation of the posterior vaginal wall opens wide the introitus, the vagina balloons out as an effect of the negative pressure, and the cervix and posterior fornix are conveniently exposed. The posterior lip of the cervix is seized with the tenaculum to immobilize it and exert countertraction in a direction opposite to that of the speculum. This serves further to steady and tense the posterior cul-de-sac and render puncture easy.

It is important to select the actual apex of the cul-de-sac as the site for puncture and to do it in the mid-line. A common error is to attempt puncture too near the cervix, or off to one side of the mid-line, with the result that the instrument enters the retroperitoneal tissue or impinges against one of the uterosacral ligaments.

After an intramucosal wheal of 1 per cent procaine has been made at the site, the trocar is thrust firmly through the cul-de-sac, angling slightly away from the sacral prominence. An audible inrush of air follows a successful puncture. (The cannula is designed to permit use of carbon dioxide as delivered by an ordinary tubal-insufflation apparatus instead of air to produce pneumoperitoneum; because the post-culdoscopy distress due to residual air is minimal, it has not been considered advantageous to use carbon dioxide.)

Occasionally, in very obese patients with large amounts of retroperitoneal fat between vaginal mucosa and cul-de-sac peritoneum, the trocar fails to penetrate the peritoneum or does so only partially. This situation is often corrected by exposure and grasping of the peritoneum with Allis clamps and completion of the opening through it with scalpel or scissors.

Visualization of the Pelvis

The excellent and complete view of the pelvic viscera obtained through the culdoscope has been most gratifying. The finer surface details of the ovaries and tubes, for example, are perhaps even more apparent than when exposed at laparotomy. Furthermore, a little experience enables one to estimate relative size with considerable accuracy. Structures that should readily be seen include the uterus, tubes, ovaries, bladder and overlying peritoneal reflection, rectum, sigmoid, distal ileal loops, appendix (often, with a little practice), ligaments, — round, uterosacral, ovarian and infundibulopelvic, — cul-de-sac floor, ureters, iliac vessels and pelvic nodes (if enlarged).

Gentle palpation of the abdomen and occasionally manipulation of the cervical tenaculum help expose the various structures. The pelvic peritoneum itself should be carefully scrutinized, particularly in the vicinity of the uterosacral ligaments and bottom of the cul-de-sac, for such an inspection often discloses unsuspected endometriosis in these areas.

Additional Culdoscopic Procedures

By means of the cervical cannula, a solution of methylene blue dye may be instilled into the uterus during the culdoscopy. If the tubes are patent the dye may actually be seen to drip immediately from the fimbriated ends. If there is tubal disease and occlusion the dye will be visible as it distends the lumen of the blocked tube or tubes, and the patho-

logical anatomy, which is often otherwise obscured by adhesions, will be clarified. This dye-insufflation test under direct vision has proved to be a valuable adjunct and is at times more accurate than a uterotubogram with lipiodol.

Biopsy, puncture of cysts and division of adhesions, as described by Decker,[1] who employs a special operating culdoscope for these manipulations, have not been attempted. Rather, the use of the culdoscope has been limited to that of a diagnostic instrument, standard approaches being preferred for any operative procedures. Although the necessary special equipment is fairly expensive, it is perfectly feasible to obtain satisfactory colored photographs through the culdoscope.

Removal of the Cannula and Postoperative Care

At the conclusion of the procedure the shoulder braces are removed, and the patient lies flat on her abdomen with the cannula still in place. Additional manual pressure on the abdomen by the culdoscopist helps express most of the remaining air as the cannula is slowly withdrawn from the cul-de-sac.

The slight distress resulting from any residual air within the peritoneal cavity rarely lasts for more than twenty-four hours and is avoided or minimized by this maneuver. The patient is also cautioned to avoid douching, marital relations or assumption of the knee-chest position for a week. Actually, the peritoneal opening is probably sealed off in a matter of hours and on several occasions has been virtually invisible at laparotomies done a day or two later. The vaginal wounds are not sutured and are healed within a week. The patients are discharged from the hospital on the following morning, unless further studies or procedures are contemplated. When indicated, laparotomy is often done immediately after the culdoscopy.

Indications

A variety of more or less obvious indications for culdoscopy may be enumerated. In addition there are many situations in a gynecologic practice that at first glance do not fall into any one of the classifications listed below. The value of culdoscopy in these situations is often appreciated only by the presentation of the clinical facts of the particular case. It is often in the approach to these problems, which are difficult to classify, that culdoscopy returns its greatest and most unexpected dividends. This nondescript field of usefulness is discovered only through experience, by having the method readily available and by a little imagination in its application.

Suspected Ectopic Pregnancy

This is one of the classic indications for culdoscopy. The difficulties of establishing a definite diagnosis in most patients with ectopic pregnancies are well known. Furthermore, many other disorders in women of child-bearing age may give rise to similar symptoms and clinical findings and do not require operative intervention. In the final analysis the presence or absence of a tubal pregnancy can only be determined by actual visualization of the tubes in most cases, and culdoscopy is a convenient and accurate solution to this vexing problem.

Slight "Adnexal Enlargement" or Indefinite Pelvic Mass Not Fixed in the Cul-de-Sac

The asymptomatic, small pelvic mass, detected perhaps on routine pelvic examination, often presents a difficult problem and must be energetically followed if ovarian neoplasms are to be discovered and treated in an early curable stage. Here, the culdoscope is chiefly of value in differentiating small, lateral fibroids, benign inflammatory masses due to the adhesions of old pelvic inflammatory disease or endometriosis or obvious small-follicle retention cysts, none of which may require surgery, on the one hand, and true ovarian tumors or cysts requiring exploration and removal on the other. One cannot, however, depend upon the culdoscope to determine whether or not an actual tumor or cyst of an ovary is definitely benign or malignant, and it is not recommended as a substitute for laparotomy in this situation.

Unexplained Pelvic or Right-Lower-Quadrant Pain, Acute or Chronic

One is frequently faced with the problem of distinguishing between appendicitis, acute salpingitis, and ruptured ovarian follicle in young women with acute pain in the right lower quadrant of the abdomen. Culdoscopic examination in such cases will avoid many unnecessary laparotomies. In the management of chronic complaints in the lower abdomen or pelvis, culdoscopy is of value in both a positive and a negative sense. Discovery of clinically undetected endometriosis or minimal chronic pelvic inflammatory disease may point the way to proper therapy. If the culdoscopic examination reveals no organic disease, both the patient and the physician are definitely reassured, and symptoms of psychogenic origin can be more effectively treated.

Sterility Problems

In patients in whom routine studies are not revealing, culdoscopy may uncover unsuspected and nonpalpable disease of the adnexa as the cause of infertility. Filmy, peritubal or ovarian adhesions secondary to minimal endometriosis, old pelvic inflammatory disease or a previous appendicitis may so interfere with ovum transport and tubal function as to prevent conception in spite of proved regular ovulation and normal tubal patency as tested by uterotubal insufflation. Correction of these situations is then often possible.

Endocrine Problems

Nearly all the endocrine disorders encountered in the female present as part of their clinical picture abnormalities of the menstrual cycle resulting from disturbed ovarian function. When the basic laboratory and x-ray studies have been completed the problem in a number of these patients resolves itself into whether the primary disturbance is in the ovary, or whether impaired ovarian function is secondary to abnormal activity in another endocrine gland, such as the pituitary or adrenal. By culdoscopy one is usually able to settle this question readily.

Culdoscopic visualization of the ovaries is a particularly helpful diagnostic aid in the study of the frequently encountered syndrome of amenorrhea (or oligomenorrhea), obesity and hirsutism, with or without a tendency to virilization. Because of the obesity the advantages of actual visualization over attempted palpation of the pelvic viscera are even more pronounced. The diagnostic possibilities under the heading of ovarian disease include the Stein–Leventhal syndrome, hyperthecosis, arrhenoblastomas and the rare hilar-cell tumors of the ovary, most of which present a characteristic appearance at culdoscopy. If the ovaries are seen to be normal (although inactive), adrenal hyperplasia or tumor must be considered.

Miscellaneous Clinical Problems

In some cases of abnormal bleeding not explained by curettage, culdoscopy might well be employed in an effort to detect an early, nonpalpable tumor of the ovary or tube. In patients suspected of having pelvic tuberculosis the diagnosis might readily be established culdoscopically.

Finally, with so much emphasis having been placed on the detection of gross pathology, the potential opportunities for the incidental or deliberate study of some aspects of the physiology of the pelvic viscera should be mentioned. Decker's observations of the contraction of the suspensory ligament of the ovary at ovulation time was a contribution to the knowledge of tubo-ovarian physiology that may be cited as an example of such an approach.[10]

Contraindications

The contraindications are actually few and are seldom encountered.

The first is a fixed cul-de-sac mass or a markedly adherent, retroverted uterus such as may be found with extensive endometriosis, which mechanically prevents free and safe introduction of the instrument. Simple retroversion, however, provided the uterus is not adherent, does not interfere with culdoscopy and is definitely not a contraindication.

Theoretically, one might occasionally encounter a patient such as one with severe cardiac disease who could not safely or comfortably tolerate the knee-chest position.

A severely contracted introitus might make culdoscopy anatomically impossible, but again this situation is seldom encountered. Finally, the occasional presence of severe acute vaginitis would warrant a temporary delay until the infection had subsided before culdoscopy was undertaken.

It should be noted that neither intrauterine pregnancy (except in later months for primarily anatomic reasons) nor acute pelvic inflammatory disease constitutes a contraindication to the procedure. Culdoscopy was performed on 9 occasions in this series in the presence of normal intrauterine pregnancy of two or three months' duration, with no complications. Culdoscopy was done frequently, wittingly or unwittingly, in the face of acute pelvic inflammatory disease, and no adverse effects on the course of the disease were observed.

Finally, mention should be made again that the procedure can be done through a virginal introitus, and that it may if necessary be used in adolescent girls, although low spinal anesthesia is usually indicated. The youngest patient in this series was a girl of fifteen, and the oldest was a woman of seventy-eight.

Complications

Potential complications include bleeding, infection and trauma to adjacent viscera, but they are rarely seen. Bleeding from the site of puncture, either immediate or delayed, occurs only occasionally, for this area is relatively avascular. Active bleeding in the operating room on withdrawal of the cannula is quickly controlled by a stitch ligature placed at the bleeding point on the puncture wound. Immediate bleeding sufficient to require suture occurred only twice in this series. In addition, 2 cases of delayed bleeding were encountered. In 1 patient a small hematoma in the retroperitoneal tissues of the cul-de-sac that was easily evacuated twenty-four hours later developed. The other patient, having been discharged from the hospital eighteen hours after an uneventful culdoscopy, had moderately severe bleeding five days later and required readmission and suture of the bleeding point. It should again be emphasized that the treatment of bleeding from the culdoscopy puncture site is suture, not packing, which accomplishes nothing but concealment of the hemorrhage.

There have been no cases of postculdoscopy sepsis as a result of contamination of the peritoneal cavity with organisms residing in the vagina. No chemotherapy has been employed before or after culdoscopy.

Finally, trauma to adjacent viscera should never occur if the operator becomes familiar with the anatomy of the cul-de-sac region, follows a technic similar to the one described, properly positions the patient and does not attempt the procedure in the presence of a fixed mass in the cul-de-sac. The rectum is really the only vulnerable organ, and only a few cases of perforation of the rectum have been reported, al-

though thousands of culdoscopies have been performed throughout the world. In each case the trocar was simply withdrawn, and no complication ensued, presumably because it was the extraperitoneal portion of the rectum that had been entered. There were no cases of trocar perforation of the rectum in this series. However, in 1 obese patient in whom initial trocar puncture was unsuccessful, a small incision was inadvertently made in the extraperitoneal portion of the rectum while the cul-de-sac peritoneum was being exposed and opened by sharp dissection. The small opening in the rectum was easily sutured, and no complications resulted. The culdoscopy in this case revealed typical Stein–Leventhal ovaries, and the patient returned a month later for bilateral ovarian wedge resection.

TABLE 1. *Indications for Culdoscopy.*

INDICATION	NO. OF CASES
Unexplained pelvic masses	29
Suspected ectopic pregnancy	43
Acute pelvic pain (other than suspected ectopic pregnancy)	6
Endocrine problems	38
Chronic pelvic pain	24
Sterility problems	10
Total	150

RESULTS OF VINCENT MEMORIAL HOSPITAL SERIES

One hundred and fifty culdoscopies have been performed in the period July, 1953, through July, 1955.

TABLE 2. *Culdoscopic Findings in 43 Cases of Suspected Ectopic Pregnancy.*

CULDOSCOPIC FINDING	NO. OF CASES
Proved tubal pregnancy	6
Negative examination (metropathia)	8*
Incomplete abortion	7†
Acute salpingitis	4
Chronic pelvic inflammatory disease	4
Normal pregnancy	6‡
Ruptured corpus luteum of pregnancy	2
Ruptured, bleeding corpus-luteum cyst	2§
Ruptured corpus hemorrhagicum	1
Endometriosis	1
Ovarian cyst	1
Stein–Leventhal syndrome	1

*3 with follicle cysts.
†Several with palpable corpus luteum.
‡2 with fibroid; 4 with palpable corpus luteum.
§Both culdoscopic errors in diagnosis.

Table 1 records the number of cases done for each of the various indications for culdoscopy in this series. The cases in which there were multiple indications for culdoscopy in the same patient are classified under the one deemed most important. A wide variety of pathologic conditions were encountered and properly identified by culdoscopy in the 143 successful examinations.

TABLE 3. *Culdoscopic Findings in 29 Patients with Unexplained Pelvic Masses.*

CULDOSCOPIC FINDING	NO. OF CASES
Uterine fibroid	7*
Ovarian cyst	5†
Endometriosis	3
Postoperative adnexal adhesions	2
Chronic pelvic inflammatory disease	1
Sigmoid diverticulitis	1
Negative result	7
Failure of procedure	3‡

*1 with endometriosis.
†2 follicle; 2 corpus luteum; 1 dermoid.
‡Extensive endometriosis.

Table 2, which presents the findings in the group of patients suspected of having ectopic pregnancy, is seen to include most of the conditions that may simulate this disease. It is particularly obvious in this group that with the help of culdoscopy prompt therapy is facilitated and both prolonged observation and an unnecessary laparotomy are avoided. It should be mentioned that patients with the so-called "classic" signs of ectopic pregnancy seen in varying degrees of shock due to brisk intraperitoneal bleeding are not candidates for culdoscopy because the diagnosis is usually obvious, and arrest of hemorrhage should be accomplished forthwith. Patients presenting this dramatic, undeniable clinical picture are actually in the minority, however.

TABLE 4. *Culdoscopic Findings in Study of 38 Endocrine Problems.*

CULDOSCOPIC FINDING	NO. OF CASES
Stein–Leventhal ovaries	15*
Probable Stein–Leventhal ovaries	7†
Atrophic ovaries	4‡
Normal ovaries	4§
Hyperthecosis of ovaries (resembling Stein–Leventhal ovaries)	3
Fromel–Chiari syndrome (resembling Stein–Leventhal ovaries)	1
Primary ovarian agenesis	1¶
Absent ovaries	1‖
Chronic pelvic inflammatory disease	1
Failure of procedure in obese, hirsute, amenorrheic, infertile patient	1

*1 with arrhenoblastoma; 2 with dermoid cysts.
†Not yet histologically verified.
‡2 with premature menopause; 1 with (?) agenesis.
§1 with Cushing's disease.
¶Skin biopsy — male.
‖Previous operation, but nature unknown before culdoscopy.

In Table 3 are grouped the culdoscopic findings in patients under study because of a pelvic mass — an

asymptomatic one in many — discovered on a routine physical examination. Again, a variety of disorders were encountered, not all gynecologic, and not all requiring therapy once a definite diagnosis had been established. Tables 4, 5 and 6 summarize the findings in the remaining patients, classified as primarily endocrine, sterility or pain problems.

As noted, there were 7 unsuccessful attempts at culdoscopy. All resulted from inability to penetrate the cul-de-sac peritoneum. None were due to technical difficulty with the instrument or electric equipment or to failure of satisfactory visualization of the pelvic organs once the culdoscope had been introduced. Subsequent laparotomies showed that 4 of the patients had extensive endometriosis, and 1 a severe chronic pelvic inflammatory process, all 5 having as a result a thickened, scarred cul-de-sac obliterated by adherent pelvic viscera, a situation not appreciated before the attempt at culdoscopy. The remaining 2 patients were very obese, and, as previously mentioned, the chief obstacle to successful cul-de-sac puncture in such patients is the thick layer of fat usually interposed between the vaginal wall and the cul-de-sac peritoneum. One need not be unduly discouraged in this regard, however, since in many obese women in this series, including 1 weighing 124.7 kg. (275 pounds), culdoscopy was easily carried out, the great majority of patients being under study for endocrine disorders.

The 2 culdoscopic errors in diagnosis in the series occurred in the group suspected of having ectopic pregnancy. A diagnosis of ruptured tubal pregnancy was made in both patients, but at laparotomy the lesion in both proved to be a ruptured corpus-luteum cyst with considerable bleeding, a large blood clot having partially surrounded the tube and ovary on the involved side.

As noted previously, there were only 2 complications in the entire series. Both were due to delayed bleeding, and neither was serious.

An attempt was made to estimate objectively the value of the procedure to both clinician and patient in expediting correct diagnosis and proper treatment in this series (Table 7).

TABLE 5. *Culdoscopic Findings in 10 Sterility Problems Not Associated with Endocrine Disease.*

CULDOSCOPIC FINDING	NO. OF CASES
Unsuspected endometriosis	2*
Large, hemorrhagic corpus-luteum cyst	1*
Unsuspected chronic pelvic inflammatory disease, with unilateral fimbrial occlusion & periovarian adhesions	1†
Negative result	5*‡

*Tubes patent by methylene blue dye test.
†1 tube patent & dilatation of other well demonstrated by methylene blue dye test.
‡Tubes patent by methylene blue dye test; 2 patients had previous uterotubograms interpreted as showing bilateral occlusion with hydrosalpinx, 2 had previous negative Rubin tests, & 1 had had tuberculous peritonitis in childhood (tuboplasty carried out 2 yr. previously, with subsequent equivocal uterotubograms).

TABLE 6. *Culdoscopic Findings in 24 Patients with Chronic Pelvic Pain and Patients with Acute Pelvic Pain Not Suspected of Having Ectopic Pregnancy.*

CULDOSCOPIC FINDING	NO. OF CASES
Chronic pain:	
Endometriosis	4*
Unsuspected chronic pelvic inflammatory disease	3
Ovarian cyst, large follicle	2
Postoperative pelvic adhesions	2†
Negative result	12
Failure of procedure	1‡
Acute pain:	
Ruptured, bleeding corpus hemorrhagicum	3
Twisted ovarian cyst	1
Negative result	1
Failure of procedure	1§

*3 unsuspected.
†1 with adherent ileum & omentum; 1 with adnexa adherent in cul-de-sac.
‡Severe chronic pelvic inflammatory disease.
§Very obese patient.

TABLE 7. *Estimate of Value of Culdoscopy in 143 Successful Cases.*

ESTIMATE OF VALUE	NO. OF CASES
Otherwise mandatory laparotomy avoided	54
Way to corrective surgery indicated	42
Positive information useful for proper medical treatment obtained	22
Valuable negative information obtained	25

CASE REPORTS

Summaries of several case histories in this series are presented as typical examples of the practical application of culdoscopy to gynecologic diagnosis. The first 3 cases illustrate the use of culdoscopy in situations that require differentiation of ectopic pregnancy and other acute abdominal conditions or painful menstrual irregularities.

CASE 1. A.G. (M.G.H. 125550), a 35-year-old para ii, gravida ii, had noted aching menstrual pains in the right lower quadrant for several years, but the periods had been otherwise normal and regular. Nine days previously, at the time of the expected period, she had experienced only slight vaginal staining for 2 days, and since then had noted almost constant right-lower-quadrant pain and slight diarrhea. Forty-eight hours before entry, the pain became increasingly severe and at the time of admission was excruciating. The appendix had been removed 13 years previously.

Pelvic examination revealed a slightly enlarged uterus with tenderness in both vaults, marked on the right. Motion of the cervix was extremely painful.

The hemoglobin was 13.5 gm. per 100 ml., and the white-cell count 10,350. Urinalysis was negative.

A diagnosis of ectopic pregnancy was strongly considered, and culdoscopy was performed to settle the ques-

tion. The uterus appeared slightly enlarged, and both tubes were visualized and found to be normal. The cause of the symptoms was seen to be a recently ruptured corpus luteum in the right ovary (the actual site of rupture in the highly colored corpus luteum was clearly visible through the culdoscope), considerable bleeding having occurred. In the light of the history and findings this was assumed to be an early corpus luteum of pregnancy. Postoperatively an Aschheim–Zondek test was positive, and the patient subsequently completed a normal pregnancy.

In this case an unusual and relatively benign complication of early intrauterine pregnancy had simulated ectopic gestation and would have led to an unnecessary exploratory laparotomy, if a more convenient means of visualizing the pelvis had not been at hand.

CASE 2. A.I. (M.G.H. 510117), a 29-year-old para ii, gravida ii, whose previous periods had been entirely normal, had noted only scant flow for 48 hours at her expected time 5 weeks previously. Profuse vaginal bleeding began 2 weeks later and continued steadily for 10 days, only to be followed by intermittent flow, becoming quite heavy 24 hours before admission. Associated with the bleeding was a constant, mid-line pain in the lower abdomen that had abruptly increased in severity just before entry. An appendectomy had been performed 11 years previously.

Physical examination disclosed tenderness suprapubically and in both vaginal vaults. The cervix seemed soft and was painful on motion; the uterus was not enlarged. There was an ill defined mass in the right vault.

The temperature was 99°F.

Laboratory studies showed a hemoglobin of 10 gm. per 100 ml. and a white-cell count of 11,300. Urinalysis was negative.

Because the possibility of ectopic pregnancy could not be ignored, culdoscopy was performed shortly after entry. The entire pelvis was seen to be bathed in thin, purulent fluid, and the ovaries and tubes were partially covered with exudate and fresh, fibrinous adhesions. Both tubes were exuding pus, and the right one was distended to several times its normal size.

In this case culdoscopy permitted rapid, definite diagnosis and prompt institution of appropriate medical therapy, avoiding an unnecessary and, in fact, harmful exploratory laparotomy, which might otherwise have been essential to rule out a possible ectopic pregnancy.

CASE 3. C.G. (M.G.H. 858561), a 25-year-old married nullipara, had experienced totally irregular periods since her menarche at the age of 13. One year previously, after a period of amenorrhea lasting for 2 years, a 6-month successful course of cyclic estrogen-progesterone therapy had been followed by 4 spontaneous normal periods. The last normal period had occurred 3 months before admission, and 2 months later there had been flowing for 2 weeks. On the day of admission she had a sudden, brisk, painless vaginal hemorrhage lasting for 1 hour. When she was seen in the office 2 hours later the bleeding had ceased; she remained asymptomatic, and examination was entirely negative except for slight tenderness in the vaginal vaults and some pain on motion of the cervix. The possible diagnoses considered were another episode of functional bleeding, missed abortion and ectopic pregnancy, and she was hospitalized for observation.

Laboratory studies were negative, and repeat pelvic examination 6 hours later showed complete disappearance of all pain and tenderness. One was almost ready to doubt the existence of any significant disease. However, because of the remote possibility of ectopic pregnancy, a semielective culdoscopy was performed 18 hours after the episode of vaginal bleeding. There was a small amount of thin, bloody fluid in the pelvis; the uterus, right tube and both ovaries were normal. The left tube, however, presented a localized area of purplish distention near its mid-portion, and a slight amount of fresh blood could be seen coming from the fimbriated end. Figure 2 shows the tiny conceptus of ectopic pregnancy removed at the subsequent laparotomy, demonstrating clearly how impossible it would have been to establish the existence of this very early tubal pregnancy by any examination other than actual visualization of the involved tube.

CASE 4. F.P. (M.G.H. 711275), a 48-year-old para iii, gravida iii, was admitted to the hospital because of attacks of colicky pain in the right flank and right lower quadrant of the abdomen, often relieved by recumbency, of 1 month's duration. Frequently associated symptoms were nausea and numbness of the skin of the right lower quadrant and right

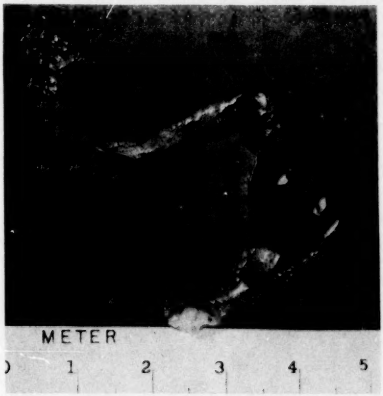

FIGURE 2. *Conceptus of Very Early Ectopic Pregnancy Removed at Laparotomy in Case 3.*

thigh. There had been mild dysuria for 1 week. There was a past history of fatty-food intolerance.

Physical examination revealed slight tenderness throughout the right side of the abdomen and in the right flank, without spasm, mass or palpable organs. Pelvic examination disclosed a small, slightly nodular, fibroid uterus, freely movable, without pain. The right vault and cul-de-sac were slightly tender, without palpable masses. Working diagnoses included ureteral stone, various adnexal disorders and cholelithiasis, and, in view of the somewhat bizarre picture, consideration was even given to the possibility of spinal-cord disease, particularly since some of the more probable conditions were excluded.

Routine laboratory studies were negative, and a cholecystogram and intravenous pyelogram were normal. Barium-enema examination was negative. Culdoscopy was performed to make the status of the pelvic viscera absolutely certain in this perplexing diagnostic problem. A small, multifibroid uterus and normal left tube and ovary were visualized, but a lemon-sized simple cyst of the ovary that had become twisted was disclosed on the right side. (The points of torsion of the tube and the ovarian and infundibulopelvic ligaments could be clearly seen through the culdoscope.) Subsequent hysterectomy and salpingo-oöphorectomy completely relieved all the symptoms.

CASE 5. I.B. (M.G.H. 839321) had been married for 8 years but had never been pregnant. A previous sterility study elsewhere was said to have been unrevealing except for failure to demonstrate tubal patency by a Rubin test. She was carefully re-evaluated along with her husband, who was found to be normal. The menstrual cycle was normal, and ovulation was shown to be occurring regularly

by basal body-temperature curves and endometrial biopsies.

Physical examination was entirely negative, as were all other studies with the exception of several Rubin tests, which were equivocal. A uterotubogram (Fig. 3) was interpreted by the X-Ray Department as follows:

> The uterus and proximal tubes appear normal. Droplets of lipiodol appear in rounded areas at the end of each tube, and 24 hours later there is a single pocket, 5 cm. in diameter. The appearance is consistent with a large cavity into which both tubes drain, and no definite free communication with the peritoneal space is demonstrated.

A laparotomy was contemplated to perform tuboplasties, but because there was no history of previous pelvic inflammatory disease and physical findings were normal,

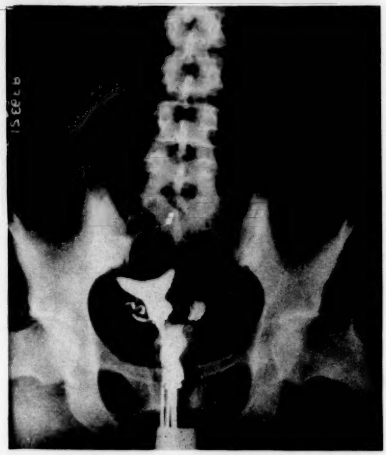

FIGURE 3. *Initial Film of the Uterotubogram in Case 5, Interpreted As Abnormal and Consistent with Bilateral Tubal Disease and Cavitation.*

culdoscopy was first performed. The uterus, tubes and ovaries were normal, and the tubes were readily proved patent under direct vision by insufflation with methylene blue dye solution. There was no sign of endometriosis, old adhesions or any other pelvic disorder.

In this case, culdoscopy proved to be a more reliable way of assessing tubal patency than hysterosalpingography, and a pointless laparotomy was avoided.

CASE 6. C.M. (M.G.H. 859903), a 32-year-old woman, complained of infertility after 4 years of marriage. The periods were regular, normal and painless, and there was no history of pelvic inflammatory disease. She had undergone an appendectomy 10 years previously and believed that a cyst of the right ovary had also been removed.

Physical examination was negative except for retroversion of the uterus. Examination of the husband eliminated him as a factor in the infertile marriage. Complete sterility studies on the patient were negative, except that during tubal insufflation, although gas seemed to pass freely, she experienced no definite shoulder pain. Culdoscopy was elected to settle the question of tubal patency and mobility and to clarify the status of the other pelvic organs. The retroverted uterus and right tube, though lying posteriorly, were well seen and appeared normal. The right ovary was absent, apparently having been totally removed at the time of appendectomy. The left ovary was large, with evidence of normal follicular activity, but was partially obscured and bound down posteriorly by adhesions. The left tube was moderately dilated and tortuous, and the fimbriated end was buried in adhesions. Insufflation of methylene blue dye under direct vision proved the right tube to be patent and demonstrated occlusion at the fimbriated end on the left, the dye filling and delineating the dilated, tortuous left tube. Laparotomy was later carried out, and the source of the many adhesions was shown to be areas of endometriosis located within them and on the hidden surfaces of the left tube and ovary. The uterus, tubes and remaining ovary were mobilized, and patency of the left tube re-established by lysis of all adhesions and excision of all gross areas of endometriosis.

In this case a silent, unsuspected lesion, producing sterility unexplained by the usual studies, was discovered by culdoscopy. As a result, the one form of therapy with any chance of success was suggested.

CASE 7. G.C. (M.G.H. 837871), a completely asymptomatic 42-year-old para ii, gravida ii, was discovered to have a right-sided pelvic mass on a routine examination. She had been having annual checkups by the same examiner for 4 years, and no abnormalities had previously been noted. The mass was firm and rounded and about the size of a lemon, and was easily palpable in the right vaginal vault. A definite connection with the uterus could not be demonstrated. The mass was considered to represent either a fibroid or an ovarian tumor, and culdoscopy was carried out to determine its exact nature. The tubes and ovaries were visualized and found normal, and the mass was seen to be a pedunculated fibroid originating from the right posterolateral uterine wall near the cornual region.

In this case, because there were no symptoms, no therapy besides routine follow-up study was necessary once the possibility of an ovarian lesion had been excluded by culdoscopy.

CASE 8. E.T. (M.G.H. 854647), a 17-year-old girl, complained of excessive weight gain over a 4-year period, facial hirsutism and severe acne for several years, as well as amenorrhea of 6 months' duration. The menses had begun at the age of 10 and had been normal until the present illness.

Pertinent physical findings included obesity, — the patient weighed 97.5 kg. (215 pounds), — a blood pressure of 190/100, generalized hirsutism, purplish abdominal striae and slight clitoral enlargement. Pelvic examination was impossible because of a virginal introitus, and even rectal examination was totally unsatisfactory because of the marked obesity. Studies of pituitary-hormone output were negative, but the urinary 17-ketosteroids were elevated (21 mg. per 24 hours). Diagnoses of adrenal hyperplasia and the Stein–Leventhal syndrome were high on the list of those considered. A presacral pneumoretroperitoneal study yielded no evidence of adrenal abnormalities.

Culdoscopy was then performed, revealing both ovaries to be typical of the Stein–Leventhal syndrome in appearance and enlarged to 3 times normal in size. Laparotomy, with bilateral ovarian wedge resection, was subsequently carried out, and the diagnosis confirmed histologically.

Culdoscopy, which provided the ultimate clue to proper diagnosis and treatment, proved to be essential in the management of this patient, in whom satisfactory bimanual pelvic or rectal examination was impossible.

SUMMARY AND CONCLUSIONS

An analysis of 150 consecutive culdoscopies per-

formed during a two-year period at the Vincent Memorial Hospital is presented. Salient features of proper culdoscopic technic are briefly described, and the various indications for the procedure are discussed in detail.

Maximum, effective utilization is aided if the procedure is kept as simple and readily available as possible and if a certain amount of imagination, seasoned by experience, is used in its application. Contraindications are seldom encountered; potential complications rarely occur, and with experience there should be very few failures or errors in diagnosis.

The wide variety of pathologic conditions identified by culdoscopy in this group of patients is tabulated according to the indications for the examination, and illustrative case summaries are presented.

This experience has convincingly demonstrated the great value of this procedure in facilitating the diagnosis of a number of gynecologic disorders. Culdoscopy frequently not only provides the clue to proper medical or surgical therapy but also makes it possible to avoid an otherwise necessary laparotomy.

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References

1. Decker, A., and Cherry, T. Culdoscopy: new method in diagnosis of pelvic disease — preliminary report. *Am. J. Surg.* **64**:40-44, 1944.
2. TeLinde, R. W., and Rutledge, F. Culdoscopy, useful gynecologic procedure. *Am. J. Obst. & Gynec.* **55**:102-116, 1948.
3. Buxton, C. L., and Herrmann, W. Analysis of one hundred culdoscopies. *Am. J. Obst. & Gynec.* **68**:786-790, 1954.
4. Noyes, R. W. Culdoscopy: advantages and limitations. *Obst. & Gynec.* **3**:184-191, 1954.
5. Thomsen, K. Die Stellung der Endoskopie in der Gynäkologie. *Geburtsh. u. Frauenh.* **14**:925-934, 1954.
6. Herstein, A. Culdoscopy — adjunct in gynecological diagnosis. *Am. J. Obst. & Gynec.* **69**:240-243, 1955.
7. Decker, A. *Culdoscopy: A new technic in gynecologic and obstetric diagnosis.* 148 pp. Philadelphia: Saunders, 1952.
8. Abarbanel, A. R. "Unexplained" infertility and culdoscopy: observations in 50 consecutive cases. *Urol. & Cutan. Rev.* **55**:339-344, 1951.
9. Palmer, R., and Palmer, E. *La Stérilité Involontaire: Évaluation des méthodes de diagnostic et de traitement.* 493 pp. Paris: Masson, 1950.
10. Decker, A. Culdoscopic observations on tubo-ovarian mechanism of ovum reception. *Fertil. & Steril.* **2**:253-259, 1951.

MEDICAL INTELLIGENCE

PIPERAZINE (ANTEPAR) NEUROTOXICITY*

Report of a Case Probably Due to Renal Insufficiency

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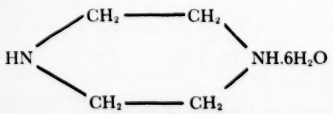
EUGENE GOTTFRIED, M.D.§

NEW YORK CITY

PIPERAZINE, available for oral use as the citrate,¶ has been found effective against pinworm and ascaris infections.[1-3] Its structural formula is as follows:



PIPERAZINE HEXAHYDRATE

Widespread experience with this compound has disclosed virtually no significant toxic manifestations at recommended doses of 50 to 75 mg. of the hexahydrate per kilogram of body weight per day, and only mild diarrhea and occasional urticaria are listed in a standard textbook of pharmacology.[4] Neurologic findings have been reported in England by White and Standen[5] and by Sims,[6] and in this country by Howie,[7] in patients taking up to three times the recommended dosage. An unusual neurologic picture accompanying the use of piperazine in an adult with renal insufficiency receiving 30 mg. per kilogram of body weight per day forms the basis of this report.

Case Report

A.C. (P.H. 125266), a 39-year-old Italian man, formerly a house painter, had been followed at the Presbyterian Hospital since January, 1953. His illnesses included chronic glomerulonephritis with hypertension (blood pressure of 190/110 to 240/140) and azotemia (blood urea nitrogen of 40 to 70 mg. per 100 ml.); Boeck's sarcoid; probable rheumatic heart disease, inactive, with mitral insufficiency; and nontoxic nodular goiter. He complained of pruritus ani for 2 years and had intermittently passed small, white worms in his stools. Repeated perianal swabs and stool specimens showed neither ova nor parasites. He finally brought in a worm identified as a pinworm, and perianal swabs disclosed similar infection of his wife and 2 children.

On June 17, 1955, the family was started on a week's course of piperazine, 20 ml. (containing 100 mg. of piperazine hexahydrate per milliliter) daily before breakfast. On June 22 the patient regurgitated his medicine and vomited twice more during the day. He felt dizzy and groggy, could not concentrate and experienced a sense of detachment. His head and extremities were tremulous; walking was unsteady and he felt clumsy and dropped objects. He omitted the drug on June 23, but progression of symptoms led to hospitalization on that day.

Physical examination showed a well developed but torpid man in no respiratory distress and able to lie flat in comfort. Although he could hear questions, as he later reported, he could not organize his thoughts and speech to answer. The breath smelled uriniferous, but no uremic frost was present. The fundi showed a Grade 2 (Keith–Wagener classification)

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¶Available as Antepar from Burroughs Wellcome and Company, Tuckahoe, New York.

retinopathy. The neck was supple. A soft nodule, 2.5 by 3.0 cm., was felt in the right lobe of the thyroid gland. Small lymph nodes were felt in the cervical, axillary and inguinal regions. The lungs were clear. The heart was enlarged, the border of percussion extending 2 cm. to the left of the midclavicular line, with a normal sinus rhythm; the sounds were of good quality, the aortic 2d sound being greater than the pulmonic. There was a harsh Grade 2 apical systolic murmur; no pleural or pericardial friction rubs were heard. Both liver and spleen were felt 4 cm. below their respective costal margins.

The temperature was 99.4°F., the pulse 88, and the respirations 20. The blood pressure was 260/150.

Neurologic examination disclosed intact cranial nerves, muscle strength and sensation. No nystagmus and no muscular fasciculations were observed. Deep tendon reflexes were active and equal bilaterally, without Hoffmann, Babinski, Chvostek or Trousseau signs. Particularly striking was a coarse, moderately violent, arrhythmic tremor involving the head and all extremities, with additional choreiform finger movements. The finger-to-nose and heel-to-shin tests were satisfactory despite interference by these tremors. The neurologist considered the abnormal movements choreiform rather than characteristic of cerebellar dyskinesia.

Laboratory data included a hemoglobin of 13 gm. per 100 ml. and a white-cell count of 6800, with 80 per cent neutrophils, 19 per cent lymphocytes and 1 per cent basophils. The specific gravity of the urine was 1.010, with a pH of 6.0, a ++++ test for protein and a negative test for glucose; the sediment contained occasional granular and hyaline casts, 3-4 white cells and 5-6 red cells per high-power field. The serum sodium was 137 milliequiv., and the potassium 4 milliequiv. per liter; the blood urea nitrogen was 68 mg., the calcium 10.1 mg., the phosphorus 8.4 mg., and the total protein 7.9 gm. per 100 ml., with an albumin of 4.4 gm. and a globulin of 3.5 gm. X-ray study of the chest revealed prominence of both hilar areas. An electrocardiogram gave evidence of hypertrophy of the left ventricle and myocardial disease. None of the results differed significantly from those of similar studies obtained in the previous May.

The patient received no specific therapy. The subjective symptoms abated overnight, whereas the abnormal movements persisted until June 25, when they began to decrease. By June 26, they had disappeared. His appetite remained good from the time of admission, without nausea or vomiting during the hospital course. With disappearance of the toxic manifestations, he appeared to revert to his status before piperazine therapy. He was discharged on June 28.

His wife and children completed the full course of piperazine therapy without incident.

The patient died on September 25, 6 hours after entering the hospital with the history and physical findings of a left-sided intracerebral hemorrhage. At autopsy a massive intracerebral hemorrhage on the left, with rupture into the ventricular system and subarachnoid space, was found. No other significant neurologic lesion was present. The other important findings included an enlarged heart (weight of 650 gm.), with hypertrophy of both left and right ventricles, and healed rheumatic endocarditis involving the mitral valve. There was severe coronary arteriosclerosis. Sarcoid granulomas and "paramyloid" material were found in the liver, spleen and lymph nodes. The kidneys showed the lesions of chronic glomerulonephritis. The parathyroid glands were hyperplastic, and there was a nodular goiter in the thyroid gland.

Discussion

Although the patient had underlying renal disease, the clinical picture was not that commonly seen in uremia and could not be attributed to altered serum calcium or potassium. Similar symptoms have been reported in patients receiving piperazine for pinworms.[5-7] In these patients toxicity was attributed to overdosage up to three times the recommended amount of 50 to 75 mg. per kilogram of body weight daily. Symptoms disappeared within a few days after the drug was stopped.

Precise data on the absorption and excretion of piperazine are lacking because there is no satisfactory method for its determination in blood, urine or feces. There is evidence that, of the piperazine absorbed, a fraction is broken down in the body and the remainder is excreted in the urine.[8] The patient described above received 2 gm. a day (30 mg. per kilogram of body weight), as did his wife and children, who remained asymptomatic. Failure to excrete the drug in the urine because of marked renal insufficiency probably accounts for the toxicity observed. The biochemical mechanism by which the symptoms were induced is not known. Whether the presence of uremia, with its heightened reactivity of the nervous system, made the patient more susceptible to piperazine is problematical. In the other reported cases with similar manifestations, no mention of accompanying renal disease was made.

Summary and Conclusions

An unusual case of piperazine toxicity, manifested by giddiness, torpor, a sense of detachment, inco-ordination and choreiform tremors, is presented. The patient was an adult being treated for pinworms. Failure to excrete the drug in the urine because of renal insufficiency was the probable cause of the toxic reaction. As with other drugs excreted by the kidney, caution should be observed in the administration of piperazine to patients with impaired renal function.

References

1. Brown, H. W. Treatment of Ascaris lumbricoides infections with piperazine. *J. Pediat.* **45**:419-424, 1954.
2. Bumbalo, T. S., Gustina, F. J., and Oteksiak, R. E. Treatment of pinworm infection (enterobiasis): comparative study of three oxyuricides. *J. Pediat.* **44**:386-391, 1954.
3. White, R. H. R., and Standen, O. D. Piperazine in treatment of threadworms in children. *Brit. M. J.* **2**:755-757, 1953.
4. Goodman, L. S., and Goodman, A. Z. *The Pharmacological Basis of Therapeutics: A textbook of pharmacology, toxicology, and therapeutics for physicians and medical students.* Second edition. 1831 pp. New York: Macmillan, 1955.
5. White, R. H. R., and Standen, O. D. Piperazine in treatment of threadworms. *Brit. M. J.* **2**:1272, 1953.
6. Sims, S. R. Piperazine in treatment of threadworms. *Brit. M. J.* **2**:1432, 1953.
7. Howie, V. M. Ten-day treatment of pinworm infection with piperazine. *Am. J. Dis. Child.* **89**:202, 1955.
8. Hanzlik, P. J. Piperazin and other organic solvents. *J. Lab. & Clin. Med.* **2**:308-327, 1917.

DOCTORS AFIELD

William Charles Wells

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SIR William Osler's respect for the Anglo-American, William Charles Wells, led him to refer to Wells as "that remarkable philosopher and physician, Wells of Charleston." Re-examination of Wells's life and work emphasizes how truly significant this man was. It is no longer important to argue which is most important in his life and work: his nationality (American), his training (Scotch-English) or his sympathies (Loyalist), or where he lived. He was a fine example of the new, vigorous, first-generation immigrant who caught the medical and cultural fires of these shores and carried them back to the Old World to become productive there. For an understanding of the intellectual ferment of Charleston, South Carolina, at the time Wells lived there, the reader should examine Johnson's *Scientific Interest in the Old South*.[1] Though the reasons for the neglect of Wells probably will never be clear, Shryock[2] having reached no firm conclusion on the matter, it is likely that such indifference was of relative unimportance to a person of Wells's stature. It may be that contemporary neglect not only spurred the man but also added ultimately to the recognition of his greatness.

Praise of Wells may be out of place, but credit for his work is not. He should be credited with the application, to the problems of medical and natural science, of the inductive method of science, as devised by Bacon, with the statement of the evolutionary doctrine of natural selection, with an explanation of the deposition of dew, with an analysis of the problem of single vision with two eyes, with the first clear statement of the clinicopathological features of "rheumatism of the heart," with the first description of the subcutaneous nodule of rheumatic origin, with the discovery of albumin and blood in the urine in scarlatinal "dropsy" and, finally, with one of the most objective, frank and fearless autobiographies ever written. Even though these broad and yet detailed contributions might be considered insufficient to assure him a place of high honor in scientific circles, this sensitive man's isolated and ethical life, one wholly devoted to medicine and science, makes his greatness secure. In this era of specialization, so necessary to an understanding of the complex phenomena of science, it pays to recall that such specialization need not destroy the breadth of one's interests in fields other than a narrow chosen one.

One hesitates to pick the *Two Essays* as being the best product of Wells's mind; yet, in a way, they come as close as any of his works to typifying his thoughts and activities. These essays are combined with the famous letter to Lord Kenyon, his statement on natural selection, and the memoir of his life in a single posthumous publication.[3]

William Charles Wells, 1757-1817, spanned some of history's most troubled years, and yet neither war nor adversity kept him from becoming a learned and productive physician and philosopher, as well as a man of "singular worth and honor."

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REFERENCES

1. Johnson, T. C. *Scientific Interests in the Old South. (Virginia University Institute for Research in the Social Sciences. Institute Monograph,* No. 23.) 217 pp. New York: Appleton-Century, 1936.
2. Shryock, R. H. Strange case of Wells' theory of natural selection. In *Studies and Essays in the History of Science and Learning Offered in Homage to George Sarton on the Occasion of His Sixtieth Birthday, 31 August, 1944.* Edited by M. F. Ashley-Montagu. 594 pp. New York: Schuman, 1944.
3. Wells, W. C. *Two Essays: One upon single vision with two eyes: the other on dew: a letter to the Right Honorable Lloyd, Lord Kenyon, and an account of a female of the white race of mankind, part of whose skin resembles that of a Negro: with some observations on the causes of the differences in colour and form between the white and Negro races of men: with a memoir of his life, written by himself.* 439 pp. London: Constable, 1818.

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 42051

PRESENTATION OF CASE

First admission. An eighteen-year-old girl was admitted to the hospital because of a nosebleed of twelve hours' duration.

A month previously she had an episode of urticaria. One week later she noted purpura, progressive weakness and pallor. There was melena for about a week before admission.

Physical examination showed a well developed, well nourished, very pale girl with purpuric spots over the extremities and buccal mucosa. There was slight nasal bleeding. Examination of the optic fundi revealed numerous retinal hemorrhages.

The temperature was 100.8°F., the pulse 100, and the respirations 22. The blood pressure was 130 systolic, 55 diastolic.

Examination of the blood showed a hemoglobin of 5.2 gm. per 100 ml. and a white-cell count of 8000. No platelets were seen in the smear. The total serum protein was 4.9 gm., the albumin 3.3 gm. and the globulin 1.6 gm. per 100 ml. Urinalysis was negative.

After transfusion with whole blood a splenectomy was performed. The spleen weighed 117 gm. and showed foci of extramedullary hematopoiesis. Postoperatively the platelets increased to normal, and the patient was discharged improved.

Second admission (six years later). Five years before admission she had an episode of jaundice. One year before entry she noted the sudden onset of bilateral painful swelling of the parotid and submaxillary glands, with dryness of the mouth and burning of the eyes. The pain subsided, but the swelling remained. Nasopharyngeal examination was negative. It was noted that the patient's eyes were dry and irritated. Sialograms showed narrowing of the parotid duct and incomplete filling of the intraglandular ducts; the alveolar system had a feathery appearance. The x-ray films of the chest, of the barium-swallow examination, of the hands and of the wrists were normal. The hemoglobin was 10.2 gm. per 100 ml. The white-cell count and platelets were normal. The total serum protein was 9 gm., the albumin 4.3 gm., and the globulin 4.7 gm. per 100 ml. Biopsy of the left parotid gland six months before admission showed chronic parotitis. Two months later, after penicillin therapy, purulent material could be expressed from both parotid ducts, but the glands remained enlarged. Three and a half months before admission the patient was irradiated with 400 r over each parotid gland and submandibular area, with marked regression in size of these glands. One month later there was an acute pneumococcal otitis media on the left, which subsided with penicillin therapy. For three months before admission the patient had noted palpitations, nervousness, tremulousness, fatigue, intolerance to heat, a 10-pound weight loss and fullness in the neck with difficulty in swallowing. Two weeks before admission there was a brief exacerbation of the swelling of the right parotid gland after extraction of a septic tooth.

Physical examination revealed a pale woman with warm, moist skin and fine tremors of the hands and legs. The parotid, sublingual and submaxillary glands were enlarged, firm and nontender. The mouth was dry. A firm, movable lymph node in the left axilla measuring 1.5 cm. in diameter was noted. The thyroid gland was diffusely enlarged to three or four times the normal size and was moderately firm; a faint bilateral bruit was audible. There was no lid lag or exophthalmos. The heart was not enlarged.

The temperature was 99.2°F., the pulse 120, and the respirations 20. The blood pressure was 135 systolic, 70 diastolic.

Urinalysis was negative; the specific gravity was 1.018. Examination of the blood revealed a hemoglobin of 9.5 gm. per 100 ml. and a white-cell count of 11,000. The total serum protein was 8.4 gm., the albumin 4.7 gm., and the globulin 3.7 gm. per 100 ml. The serum nonprotein nitrogen, calcium, phosphorus, phosphatase, fasting blood sugar, amylase, uric acid and prothrombin content were normal. The basal metabolic rate was +36 per cent.

The patient was discharged on the fourteenth hospital day on methyl thiouracil.

Third admission (one month later). During the three weeks before admission she experienced intermittent pain in the right parotid gland associated with a maximum temperature of 101°F., especially at night. Five days before entry methyl thiouracil was discontinued, and the tenderness diminished. On the night before admission she complained of malaise, anorexia, shaking chills, a parched throat and stiffness of the neck. The temperature was 102.6°F.

Physical examination showed a pale, restless, critically ill woman complaining of headache and fever. There was a prominent cardiac apical impulse. Other findings were the same as during the previous admission.

The temperature was 105.4°F., the pulse 140, and the respirations 32. The blood pressure was 80 systolic, 50 diastolic.

Examination of the blood showed a hemoglobin of 12.5 gm. per 100 ml. and a white-cell count of 38,500, with 96 per cent neutrophils. The nonprotein nitrogen was 16 mg., the total protein 7.7 gm., the albumin 4 gm., the globulin 3.7 gm., and the bilirubin 2.8 mg. direct and 6.8 mg. total per 100 ml. The cephalin flocculation was ++ in forty-eight hours, the thymol turbidity 9.3 units, the thymol flocculation +, and the alkaline phosphatase 8.6 units. The prothrombin content was normal. Blood culture grew out meningococci, Type 1. The urine gave a +++ test for albumin and had a specific gravity of 1.022; the sediment contained 0 to 2 white cells and 2 to 3 granular casts per high-power field.

The patient was given intravenous infusions of fluid, including 500 ml. of whole blood. With penicillin therapy the temperature returned to normal, but icterus persisted for four or five days. She was discharged improved on the fifteenth hospital day and started on potassium iodide.

Fourth admission (two months later). A subtotal resection of the thyroid gland, which showed hyperplasia with slight involution, was performed. The hemoglobin was 11 gm. per 100 ml. The total serum protein was 8.1 gm., the albumin 3.9 gm., the globulin 4.2 gm., the calcium 11.6 mg., the phosphorus 3.8 mg., and the nonprotein nitrogen 24 mg. per 100 ml. The cephalin flocculation was + in forty-eight hours, the thymol turbidity 7 units, and the thymol flocculation +++. Bromsulfalein retention was 32 per cent in fifty-five minutes. A tuberculin skin test (O.T. 1:1000) was negative. An x-ray film of the hands was normal. The postoperative course was uneventful.

Fifth admission (six years later). The patient was now thirty years old. In the interval mild hypothyroidism requiring a maintenance dosage of thyroid developed. About four years before admission, the parotid, submaxillary and sublingual glands were noted still to be enlarged and firm. There was considerable saliva in the mouth, and the oral mucous glands appeared to be increasing in size. Thirty-one months before entry she was said to have had a urinary-tract infection, with low-back pain. Fifteen months later each parotid and submaxillary gland was irradiated with 200 r, with no response. One year before admission there was an episode of left-sided "pleurisy." Seven months before admission, because of increased bilateral parotid and submaxillary swellings that failed to respond to cortisone therapy, these areas were irradiated with 1000 r, with no change in the size of the glands. At this time the previously noted lymph node in the left axilla had increased to 2.5 cm. in diameter; a similar node measuring 2 cm. in diameter was felt in the right axilla. Six weeks before entry there was increased swelling and tenderness of the left submaxillary gland accompanied by a temperature of 99.4°F. The lymph node in the left axilla now measured 3 cm. in diameter. Two weeks later the patient noted malaise, cervical lymphadenopathy, a temperature of 100°F., dark urine and puffiness of the ankles and hands. The urine appeared normal after a week. The ankle swelling, which was most marked in the evening, persisted and ten days before admission involved both hips. Six days later the temperature was 100°F. With diuretic therapy the edema of the thighs subsided, but the low-back pain recurred and was more severe. On the day before admission there was difficulty in breathing because of progressive sharp pain in the left side of the chest, which was aggravated by coughing or sneezing, and the temperature again rose to 100°F. There was an episode of vomiting, and dark urine was noted.

Physical examination showed, in addition to previous findings, moderate left-costovertebral-angle tenderness, a liver edge palpable 1 fingerbreadth below the right costal margin and slight ankle edema. One observer noted left plantar extension.

The temperature was 101.2°F., the pulse 104, and the respirations 24. The blood pressure was 98 systolic, 54 diastolic.

The urine gave a ++++ test for albumin and had a specific gravity of 1.043; the sediment contained 0 to 3 red cells, 2 to 7 white cells and 0 to 1 hyaline and 0 to 3 granular casts per high-power field. The urea clearance was 76 per cent. A twenty-four-hour urine specimen contained 5 gm. of protein. The phenolsulfonphthalein excretion was 28 per cent in fifteen minutes and 58 per cent in two hours. Examination of the blood revealed a hemoglobin of 9 gm. per 100 ml. and a white-cell count of 20,000, with 89 per cent neutrophils. The reticulocyte count was 1.5 per cent. The serum nonprotein nitrogen was 36 mg., the cholesterol 281 mg., the calcium 8 mg., the phosphorus 4.8 mg., the uric acid 5.2 mg., the total protein 4.7 gm., the albumin 1.8 gm., the globulin 2.9 gm., and the bilirubin 0.5 mg. per 100 ml. The alkaline phosphatase was 2.2 units. The serum iron was 50 microgm; and the total iron binding capacity 250 microgm. per 100 ml., and the iron saturation 20 per cent. The serum electrophoretic pattern showed 23 per cent albumin (normal, 48 per cent), 10 per cent alpha-1 globulin (normal, 7 per cent), 24 per cent alpha-2 globulin (normal, 9 per cent), 21 per cent beta globulin (normal, 14 per cent) and 22 per cent gamma globulin (normal, 22 per cent). The Congo-red test revealed 66 per cent retention. The patient was Rh negative. She had never been pregnant. Coombs tests were positive. The cold-agglutinin titer was 1:2. The antistreptolysin titer was less than 100. The bone marrow showed hyperplasia. The prothrombin content was normal. Four "L.E." preparations, the blood Hinton test and blood and urine cultures were negative. X-ray films of the chest demonstrated ill defined densities lateral to the heart

borders, an increased density posterior to the heart, hazy areas of increased density at both lung bases, marked pleural thickening at the left costophrenic sulcus and a slightly elevated left leaf of the diaphragm, which showed minimal movement. Biopsy of the enlarged lymph node in the left axilla demonstrated amyloidosis.

The patient continued to be febrile and weak, with moderate pleuritic pain in the left side of the chest and slight epigastric tenderness. After antibiotic therapy and blood transfusions there was symptomatic improvement. X-ray films of the chest at first showed an increase in density in the left lower lobe and then some clearing of this process. On the eighteenth hospital day there was left infrascapular and flank pain; the temperature rose to 103°F.; the pulse was 134, and the respirations 28; the hemoglobin fell to 6.5 gm. per 100 ml., and the reticulocyte count was 3.4 per cent. After transfusions the hemoglobin rose to 9 gm. per 100 ml. Two days later there was pain in the right side of the chest, with tachypnea. Later that night the patient was awakened by severe pleuritic pain anteriorly in the right lower portion of the chest. There was profuse sweating, calf tenderness and enlargement of the heart. A persistent friction rub was heard over the right side of the chest. The temperature was 102°F., the pulse 160, the respirations 64, and the blood pressure 80 systolic. An x-ray film of the chest demonstrated a large area of hazy density in the right lower lobe. An electrocardiogram showed a normal sinus rhythm at a rate of 125; the P waves were slightly peaked in Lead 2, the PR and QRS intervals were 0.16 and 0.08 second respectively; and the T waves were flat in Leads aVF and V_6. By the twenty-seventh hospital day there was symptomatic improvement although the temperature ranged between 99.2°F. and 100.4°F. X-ray films of the chest revealed the previous areas of increased density to be clearly defined and smaller. There was a new area of infiltration extending out from the left hilus and a small amount of fluid in the left pleural cavity. The patient began to ambulate on the forty-second hospital day. During the fifth hospital week the hemoglobin again fell to 6 gm. per 100 ml., and the reticulocyte count was 4.2 per cent. After transfusions the hemoglobin rose to 12 gm. per 100 ml. on the fifty-fifth hospital day. During the first sixty-three days in the hospital the edema extended to the level of the sixth ribs. The patient had gained 38 pounds in weight. The total serum protein fell to 3.7 gm.; the albumin was 1.1 gm., and the globulin 2.6 gm. per 100 ml. The serum cholesterol rose to 473 mg. per 100 ml. The serum bilirubin and nonprotein nitrogen remained normal. The urine on the sixty-fifth hospital day gave a ++++ test for albumin, and had a pH of 6.5; the sediment contained 3 to 5 red cells, 4 to 8 white cells and 2 to 4 hyaline and granular casts per high-power field with lipoid droplets. A twenty-four-hour specimen of urine (2980 ml.) contained 100 milliequiv. of sodium and 36 milliequiv. per liter of potassium and 0.3 gm. per 100 ml. of protein. With a low-sodium diet and diuretic therapy the peripheral edema and ascites were greatly reduced, and the patient lost 24 pounds in weight. A urine concentration test on the seventy-seventh hospital day showed a specific gravity of 1.022. The temperature returned to normal. She was discharged on the eighty-first hospital day.

Sixth admission (eleven days later). Ten days before admission, while the patient strained at stool, a sharp, nonradiating, substernal pain relieved by bed rest developed. A substernal discomfort, accentuated by coughing, persisted. During the week preceding admission she noted progressive weakness and exertional dyspnea necessitating bed rest for three days before entry. The weight had remained the same since the previous discharge.

Physical examination showed a pale, tachypneic woman with edema over the lower abdomen, sacrum and lower extremities. Deep tendon reflexes were normal. Other findings were as previously noted.

The temperature was 101.2°F., the pulse 108, and the respirations 28. The blood pressure was 120 systolic, 60 diastolic.

Examination of the blood showed a hemoglobin of 5.8 gm. per 100 ml., a white-cell count of 32,000 and a reticulocyte count of 28 per cent. The urinary findings, total serum protein, albumin and globulin were essentially the same as before. An x-ray film of the chest showed multiple areas of ill defined increased density in both lower-lung fields.

With blood transfusions and high dosages of cortisone the hemoglobin rose to 10.1 gm. per 100 ml., and the patient was discharged on the twenty-third hospital day.

Final admission (two days later). For two days she had noted increasing cough, shortness of breath, shaking chills and sharp pain in the right side of the chest anteriorly.

Physical examination showed an acutely ill, gaunt, markedly dyspneic, pale woman. Examination of the chest revealed dullness at the lung bases and bilateral coarse rales. The heart was enlarged. There was pitting edema of the ankles and legs. Otherwise, findings were as previously noted.

The temperature was 101°F., the pulse 156, and the respirations 44. The blood pressure was 95 systolic, 60 diastolic.

Urinalysis showed the same findings previously noted. Examination of the blood revealed a hemoglobin of 7 gm. per 100 ml. and a white-cell count of 30,000, with 95 per cent neutrophils. The serum nonprotein nitrogen was 60 mg., the total serum protein 4.2 gm., the albumin 2 gm., the globulin 2.2 gm. and the cholesterol 276 mg. per 100 ml. An x-ray film of the chest demonstrated, in addition to previous findings, a large area of patchy density in the sub-

apical segment of the right lower lobe and scattered smaller densities, the largest of which was in the apical segment of the right lower lobe. Throat culture grew out abundant pneumococci and moderate *Staphylococcus aureus*. Blood culture grew out pneumococci.

With antibiotic therapy, oxygen, blood transfusions and cortisone, the temperature returned to normal levels, the x-ray film of the chest showed partial clearing of the lungs, and the hemoglobin rose to 12 gm. per 100 ml. Mild calf tenderness was noted on the fifth hospital day. Paranoid psychotic behavior occurred. On the tenth hospital day there was a sudden episode of unresponsiveness, with the eyes turned to the left and upward, the arms semiflexed on the trunk, the hands clenched, with the fingers extended downward, and the legs straight and stiff, with the toes partially flexed. There were fine, rapid tremors with increased tone in the upper and lower extremities. No cranial-nerve abnormalities were detected. No Trousseau sign could be elicited. No plantar response was obtained, but all other reflexes were hyperactive. There was no response to painful stimuli. The serum nonprotein nitrogen was 73 mg., and the calcium 6.4 mg. per 100 ml.; the serum sodium was 138 milliequiv., the potassium 4.9 milliequiv., the chloride 106 milliequiv., and the carbon dioxide 17 milliequiv. per liter. The patient responded to intravenous administration of fluid and calcium gluconate. About two weeks after admission a severe stomatitis developed. Culture grew out *Staph. aureus* and nonpathogenic candida. Antibiotic therapy was stopped, and the stomatitis subsided. There was a persistent *Proteus vulgaris (Bacillus proteus)* urinary-tract infection. By the nineteenth hospital day, the serum nonprotein nitrogen had returned to normal, and the cholesterol was 276 mg. per 100 ml. Ten days later the hemoglobin had fallen to 8 gm. per 100 ml., and the patient again became febrile. The total serum protein ranged between 3 and 4.2 gm. per 100 ml., with an albumin-globulin ratio of 0.3:0.9; the cholesterol was 382 mg. per 100 ml. on the forty-fifth hospital day. The peripheral edema diminished but never cleared completely. On the sixtieth hospital day the patient complained of diffuse abdominal pain. Examination of the abdomen showed diffuse mild tenderness without rebound tenderness. She died four days later. Terminally, there were episodes of irrational speech.

Differential Diagnosis

Dr. Maurice B. Strauss*: May I see the x-ray films?

Dr. C. C. Wang: The films of the chest taken approximately six years before the patient's death show perfectly clear lung fields and a normal heart shadow. On a film, taken six months before death, there is a large area of infiltration in the left lower lobe, which appears somewhat reduced in size. The remaining lung fields are clear. Approximately ten days later the infiltration in the left lower lobe has cleared; there is now a large area of infiltration in the right-lower-lung field. In progressive films the infiltration in the left lower lobe clears, as does the infiltrate on the right. The films taken shortly before death, however, show the presence of some pulmonary involvement bilaterally.

Dr. Strauss: Do the bones appear to be normal?

Dr. Wang: The bones are normal. There is edema of the chest wall. I saw the films of the hands, which show no abnormality.

Dr. Strauss: This patient suffered from purpura and subsequently had many visceral disorders. "The Visceral Lesions of Purpura and Allied Conditions" was the title of Sir William Osler's[1] last publication upon a subject that interested him greatly over several decades and on which he wrote repeatedly. It must be noted that none of his cases were quite as complicated as the one now under consideration. I am sure that he would have delighted in this Case Record, and in all sincerity I must express my regret that he is not here today to discuss it in my place.

Thrombocytopenic purpura may follow various infections, may be a manifestation of diverse drug and other sensitivities, may complicate or precede disseminated lupus erythematosus by years or may appear as a condition of unknown etiology, when like so many obscure and idiopathic syndromes it is referred to by an eponym — Werlhof's disease. This disorder occurs most often in young people, with females suffering two to four times as frequently as males. After removal of the spleen more than two thirds of the patients become and remain asymptomatic, although thrombocytopenia may recur. It must be noted, however, that the majority of patients, particularly the young ones, undergo spontaneous remission, many never having a recurrence. Whether the etiology in these patients differs from that in those who have either a chronic or a recurrent course is not clear. However, unless impending catastrophe threatens, I prefer not to recommend removal of the spleen until it becomes apparent that the disorder is chronic or recurrent and that no etiology can be found.

Thrombocytopenic purpura may also be a manifestation or concomitant of a variety of hematopoietic disorders, including leukemia, lymphoma, Hodgkin's disease, aplastic and other anemias, multiple myeloma and mononucleosis, as well as of such diseases as tuberculosis, disseminated lupus erythematosus and sarcoidosis among others. There was no evidence for such a disorder on the first admission, although the finding of foci of extramedullary hematopoiesis in the spleen is so highly unusual in idiopathic thrombo-

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cytopenic purpura that suspicion must be aroused that the disorder in this case was a manifestation of some underlying process. I am assuming that the microscopical interpretation was correct and that the lesion seen was not a specific infiltration. The thrombotic variety of thrombocytopenic purpura, generally associated with hemolytic anemia and neurologic manifestations as well as with a fatal outcome within a matter of months, may have such splenic hematopoietic foci. It is my impression that this disorder belongs in the group of vascular diseases, including arteritis and disseminated lupus erythematosus. As a matter of fact all purpuras must have a vascular abnormality of some form.

It is to be emphasized that the temporal sequence of remission after removal of the spleen does not indicate causality. It may also be noted parenthetically that in Werlhof's disease the spleen is seldom more than slightly enlarged — often it is not palpable on physical examination — whereas in many secondary types it may be considerably enlarged.

The jaundice, which occurred a year later, may have been an incidental attack of infectious hepatitis or possibly of a hemolytic nature.

Five years after the bout of purpura bilateral salivary-gland enlargement, dryness of the mouth and burning of the eyes developed. I regret that I cannot avoid the use of eponymic designations. Possibly I should go all-out since we have Graves's and Bright's disease in the offing, and even at this point, on the basis of the parotid-gland biopsy, I must exclude Heerfordt's uveoparotid fever (now believed to be due to Boeck–Besnier–Schaumann sarcoidosis). Salivary-gland and lacrimal-gland enlargement of this sort has commonly been known as Mikulicz's disease or, when due to a recognized type of infiltrative tissue (leukemia, Hodgkin's disease, sarcoidosis and so forth), as Mikulicz's syndrome. The keratoconjunctivitis sicca, studied most intensively by ophthalmologists and often associated with salivary-gland enlargement, goes by the name of Sjögren's syndrome. Morgan and Castleman,[2,3] in this laboratory, have studied the microscopical findings of these disorders extensively and have concluded that the changes in the salivary glands are identical in the two conditions. They believe that Mikulicz's disease may be a less highly developed variant of the larger symptom complex, Sjögren's syndrome, and that both may be of systemic origin. These manifestations characteristically occur in middle-aged women, often after the menopause, although males are afflicted. Morgan[3] has reported a case in a fifteen-year-old boy as well as the present case in a woman of twenty-three years. An association with rheumatoid or degenerative arthritis is frequent. A patient with Sjögren's syndrome whom I saw in consultation at this hospital four years ago was a woman who later died of disseminated lupus erythematosus and was the subject of one of these exercises.[4] History is known for its repetitiousness. The microscopical diagnosis of "chronic parotitis" in the present case is surprising, but I shall adhere to the belief that this case typifies the Mikulicz–Sjögren syndrome.

The development of Graves's disease, manifested by goiter, palpitation, nervousness, tremulousness, fatigue, heat intolerance and weight loss, together with tachycardia and an increased rate of oxygen consumption, hardly requires comment. After suitable medical preparation, complicated by an intercurrent meningococcemia, the patient successfully underwent subtotal thyroidectomy and subsequently exhibited mild hypothyroidism requiring thyroid replacement therapy. The microscopical changes in the thyroid gland were those anticipated. I must consider this affair as incidental to the ultimate disorder, although an association with idiopathic thrombocytopenic purpura has been noted by Castle[5] and others and the elevated globulin already present may have had a bearing on thyroidal hormone transport.

The next episode that I shall consider occurred six years later, or approximately twelve years after the purpura, the patient now being thirty years of age. The occurrence of extensive edema, marked albuminuria, severe hypoalbuminemia, minimal formed elements in the urinary sediment and good renal function evidenced by concentrating ability, urea clearance and phenolsulfonphthalein excretion spells the nephrotic syndrome. (The specific gravity of 1.043 can only be partly accounted for by the one point added by each 0.4 gm. per 100 ml. of protein in the urine and was unusually high.) The serum cholesterol varied from time to time, probably in part as a result of changing nutritional status and in part possibly from changing metabolic and thyroid status.

What caused the nephrotic syndrome? Glomerulonephritis is most commonly responsible; syphilis and bilateral renal-vein thrombosis are least common. Disseminated lupus erythematosus, amyloid kidneys and diabetic nephropathy may be responsible. The Hinton test on the blood was negative. A positive test would, however, incline me to believe it was the biologically false-positive reaction of disseminated lupus erythematosus rather than indicative of syphilis. Four "L.E." preparations were negative. Against glomerulonephritis were the low antistreptolysin titer, the few formed elements in the sediment and the lack of evidence of conspicuous glomerular involvement other than proteinuria. The Congo-red test was not discriminating, but the biopsy of the lymph node showed amyloidosis, so that I shall rest on this as an explanation for the nephrotic syndrome. I am relying completely on the pathologist's ability to differentiate amyloid from the paramyloid, which Teilum[6] finds in systemic lupus erythematosus.

At one time or another there was evidence of pleuritic pain on both left and right sides and on one occasion a suggestion of pericardial involvement, again suggesting lupus erythematosus. Pulmonary

changes on x-ray examination were at first in the left and then in the right lower lobe. These became less marked as the left hilar region became infiltrated. Then there were multiple areas of ill defined density in both lower-lung fields. Later there was a new area in the subapical segment of the right lower lobe and then a large infiltrate in the apical segment. Various granulomatous processes, including the popular Wegener process, come to mind; however, these lesions seemed to clear completely. Pneumococci predominated in the sputum and were grown from the blood. Some of the pulmonary findings may have resulted from embolic infarction from the legs since there was tenderness of the calves. However, there was nothing specific in the x-ray examination. The peaked P waves in Lead 2 are consistent with pulmonary embolization. Nevertheless, I believe that a pneumonic process played a considerable part in the picture, possibly assisted by specific infiltrations, very possibly of amyloid or lupus erythematosus.

Throughout this record the history of bacterial infection repeated itself like the minor theme of a sonata: acute pneumococcal otitis media, acute meningococcemia, urinary-tract infections, pleural and pulmonary involvement, pneumococcal bacteremia and, finally, what may have been terminal peritonitis. Agammaglobulinemia comes to mind, but the quantitative analysis of the plasma proteins eliminates it from further consideration. The susceptibility of patients with leukemia and allied conditions to infections remains a mystery, but in general the course of events and offending organisms are not like those in this case. Multiple myeloma, which is often accompanied by an elevated gamma-globulin level but is rare at this age, appears to be a common predisposing cause of recurrent, particularly pneumococcal, infection. A recent publication[7] indicates 44 pneumonic episodes in 10 patients. Three had pneumococcal bacteremia. In 4 others the pneumococcus was isolated only from the sputum. One patient had 13 bouts of pneumonia. First one area and then another may be the seat of consolidation. Poor antibody response to both natural and experimental antigenic challenge has been demonstrated in myelomatosis and a qualitative abnormality of gamma globulin suggested. It is of interest that individual bouts of infection generally respond well when specific antibiotic therapy is employed, but often an identical organism is found to be responsible for a subsequent episode.

The pattern of serum globulin abnormality in multiple myeloma varies greatly. A specific elevation in the gamma-globulin fraction (M-protein) is most diagnostic. Rarely is the alpha fraction involved. Abnormalities in the beta fraction are fairly common but not specific. From the second serum protein determination when the patient was twenty-four years old it may be noted that there was an absolute and relative increase in the globulins.

Many systemic disorders of obscure etiology are associated with altered serum globulins, particularly elevation of the alpha-2 and gamma components. A relation to hypersensitivity has been suggested for a number of these conditions, and the role of the globulins in antigen-antibody reactions pointed out. The greatly increased use of drugs of all sorts, including antibiotics and sulfonamides, has been considered of probable significance in connection with the supposedly greater incidence of these systemic disorders. The occurrence of hyperglobulinemia eventually followed by amyloidosis in horses immunized against diphtheria is well known. The "L.E."-cell phenomenon, as well as the Coombs test, appears to be due to abnormal serum components, the former in the gamma-globulin area. The biologically false-positive serologic tests for syphilis likewise appear with altered serum proteins, particularly with elevated globulins. Teilum[6] believes that the material that he terms paramyloid results from an allergic hyperglobulinosis, and notes its occurrence in a number of disorders. Only after the development of the nephrotic syndrome was an analysis of the individual globulin components available presumably since this procedure was not being done at an earlier date. The absolute values — approximately 1 gm. per cent for alpha-2, beta and gamma globulins — were reasonably normal, although the alpha-2 level was a trifle elevated since it is generally conceded that the maximum normal value is 0.8 gm. This has been reported in amyloidosis as well as with almost all the disorders under consideration here.

Amyloidosis is said to occur in about 5 to 15 per cent of cases of myeloma, and conversely myeloma or plasmacytosis has been found in as high as 20 per cent of cases of so-called "primary" amyloidosis. However, amyloidosis has been associated with Hodgkin's and other lymphomas, with leukemia and with many chronic infections, particularly when these are associated with increased serum globulin levels. I have yet to hear of its occurrence with disseminated lupus erythematosus, but there must always be a first time. Although some students are able to differentiate "primary" and "secondary" deposits of amyloid on the basis of staining reactions, I am not convinced. The distribution of the deposits in cases that are chronologically secondary to chronic suppurative disease overlaps the distribution found in cases in which there is no apparent cause, so that I have seen "primary" amyloidosis with the characteristic distribution of the secondary type and vice versa. Analyses such as those recently carried out at this hospital may eventually clarify this situation. Although amyloid may be limited in its distribution, particularly in primary cases, it most often involves a great many tissues. Unless "secondary contraction" of the kidneys occurs, uremia is rare, and hypertension very uncommon. In contrast, the "myeloma kidney" frequently leads to

renal failure although hypertension is almost never found.

The various turbidometric and flocculation tests in this case are of little assistance. They presumably reflected the altered serum protein constituents. The marked leukocytosis and neutrophilic predominance encountered so frequently do not necessarily implicate a bone-marrow disorder. Although leukopenia of note is found in the overwhelming majority of the cases of systemic lupus erythematosus at one time or another, leukocytosis, particularly in response to infection or after the use of steroid hormones as great as in this case, may be found. The rapidity with which the hemoglobin level fell, the reticulocytosis and the positive Coombs test implicate a hemolytic process. The early slight elevation of serum calcium and the later low level may be correlated with the serum protein changes. I cannot decide whether the preterminal neurologic manifestations were in fact due to a depressed level of ionized calcium (they appeared to be tetanic and to respond to calcium administration) or whether there was mischief in the brain.

At this point I should like to ask two questions. Was the urine examined for Bence-Jones protein?

DR. RICHARD B. COHEN: I believe that it was and that it was negative.

DR. STRAUSS: Was a bone survey made that may have indicated osteolytic lesions or osteoporosis?

DR. COHEN: None of the x-ray examinations of the bones showed any abnormality.

DR. STRAUSS: Although Bence-Jones protein is not specific, its presence would strongly suggest that a myelomatous or lymphomatous process was the underlying disorder. Without such confirmatory evidence I can merely be highly suspicious since generalized systemic amyloidosis could account for the late phenomena. So could other diffuse vascular disorders, including systemic lupus erythematosus, for which a case could be elaborated in spite of the absence of joint pains, renal failure and skin rashes other than the initial purpura.

My final diagnoses, then, must include Werlhof's disease treated by splenectomy, Graves's disease treated by thyroidectomy, postoperative hypothyroidism, Mikulicz–Sjögren syndrome, hemolytic anemia, pulmonary infection and probably infarction and the nephrotic syndrome. I believe that generalized systemic amyloidosis can account for many of the events, but I wonder whether there was not an underlying or concomitant systemic disorder such as myelomatosis, one of the lymphomatous diseases or a disseminated vascular process such as lupus erythematosus.

DR. COHEN: Dr. Du Toit, do you care to comment on the protein studies that were done?

DR. CHARLES H. DU TOIT: I think that Dr. Strauss's analysis covers all I could possibly say. The electrophoretic pattern of the serum was typical of the nephrotic syndrome, regardless of what the etiology may have been. The electrophoretic pattern of the urinary proteins was likewise done and was also in keeping with the nephrotic syndrome; it did not give any evidence of myeloma proteins.

DR. COHEN: Dr. Ropes, you were one of the few physicians who did not see this patient in the hospital; have you any comment?

DR. MARIAN W. ROPES: I heard many of the discussions at the time of the hospital admissions but did not see the patient. I agree with Dr. Strauss that there was an underlying generalized systemic disease. I do not know the answer, and would place, in somewhat different order, the systemic diseases that Dr. Strauss listed.

DR. BERNARD M. JACOBSON: I should like to congratulate Dr. Strauss on this vivid, clear analysis of the various possibilities in a complicated case. During the patient's terminal illness on the sixth admission, when she was severely anemic and had a positive Coombs test, a bone-marrow aspiration showed a mild erythroid hyperplasia, and nothing whatever to suggest multiple myeloma. Dr. Strauss, would you still consider myeloma as an underlying disease in the face of that bone-marrow picture?

DR. STRAUSS: I should not exclude it on the basis of a bone-marrow puncture.

DR. JACOBSON: In our experience a strong hemolytic component is rare in myeloma in comparison with its frequency in leukemia and lymphoma.

DR. STRAUSS: I listed three diseases as possible underlying disorders; I have no great preference for any one of the three. I see nothing in the fact that there was a hemolytic anemia to prejudice me one way or the other.

DR. JACOBSON: It might be noted that several descriptions of blood smears, and one platelet count, contained in the record, agree that the platelets were markedly increased. I suspect that this thrombocytosis can be ascribed to the postsplenectomy state and to the hemolytic disease. This thrombocytosis may well be a factor in the thrombotic episodes that have been postulated.

DR. DAVID WEISBERGER: I saw this patient originally for the bilateral parotitis. At that time we studied her for many diseases, none of which were found. The first film of the chest was taken to see whether she had sarcoidosis or tuberculosis. She was the first patient — we now have seen 4 others — in whom salivary-gland disease was followed by hyperthyroidism. What significance that combination has I do not know.

DR. COHEN: Dr. Calkins, you know a great deal about amyloid disease; do you have a comment?

DR. EVAN CALKINS: I should certainly agree that primary and secondary amyloidoses have been separated more clearly than is justified on the basis of

their respective sites of deposits without further knowledge of their chemical characteristics.

DR. COHEN: You think, then, that the amyloidoses may be a spectrum of entities rather than just two, sharply divided by distribution and that there is a considerable overlap. Is that true chemically as well as morphologically?

DR. CALKINS: I cannot say, because I have not looked at enough varieties of amyloidosis. Certainly, several characteristics seem to be present in different degrees in different tissues that we have examined. I think not only that amyloid from one patient is composed of a number of different materials but also that amyloid from different patients is different.

I think Dr. Strauss's discussion was excellent. I agree that all the later manifestations of the case could have been on the basis of amyloidosis. I am interested to know whether Dr. Strauss is willing to select the one of the various underlying possibilities that he would consider the most likely.

DR. STRAUSS: That would be difficult because there are cogent arguments against each one.

DR. JACOBSON: Dr. Du Toit, what was the clinical impression at the time of the last admission?

DR. DU TOIT: We considered about the same possibilities that Dr. Strauss has outlined. A number of us were quite strongly inclined toward lupus erythematosus, but persistence in seeking the lupus-cell phenomena did not bear this out. I do not have anything more to contribute that Dr. Strauss has not completely covered.

DR. E. P. TUTTLE, JR.: I think there is a possibility that the patient had liver disease dating from the episode of jaundice early in the course and continuing to the end as scarring. This may have joined with the proteinuria to cause the late drop in globulins. If the liver was diseased, the blood urea and nonprotein nitrogen, which were taken to indicate good renal function until near the end of the illness, would be less reliable indexes. She would have been making less urea.

DR. COHEN: Do you believe the liver disease was amyloidosis?

DR. TUTTLE: The acute episode of jaundice suggested hepatitis. I think that there may have been scarring secondary to that and amyloid in the liver as well at the time of death.

DR. STRAUSS: If she was not converting dietary protein to nonprotein nitrogen, what was she doing with it?

DR. TUTTLE: It is our impression that patients with liver disease have low blood urea levels. The blood amino acids are elevated, but usually not enough to restore the nonprotein nitrogen to normal. The explanation for this may be the reduced protein intake secondary to the anorexia of liver failure or the utilization of alternate pathways of nitrogen metabolism, as with the formation of ammonia in the blood.

DR. BENJAMIN CASTLEMAN: Perhaps Dr. Maloof would comment on the relation of the disease in the salivary glands to the hyperthyroidism.

DR. FARAHE MALOOF: Dr. Weisberger's observation about the development of hyperthyroidism in 4 patients who previously had salivary-gland trouble is quite interesting. Whether there is a causal relation remains to be proved.

It is well known that iodides are concentrated by the salivary glands and are found in saliva. However, the recent data of Kirkwood and Fawcett[8] suggest a more important relation between the salivary glands and iodine metabolism. These authors reported that the salivary glands of rats were able to deiodinate di-iodotyrosine, and hence suggested that the salivary glands were "reverse thyroid glands" — that is, the thyroid gland made thyroid hormone and the salivary gland broke it down. This appears quite relevant to the present discussion, except that di-iodotyrosine is not generally found in the serum of patients. Since thyroxine and tri-iodotyronine are assumed to be the major active circulating thyroid hormones, it would be relevant to determine whether they are deiodinated by the salivary glands. It is also disconcerting to find that Tong et al.[9] have been unable to confirm the work of Kirkwood and Fawcett. In spite of this, further studies of iodine metabolism may prove fruitful in patients with salivary-gland disease, especially since the salivary-gland enlargement may be only a focal manifestation of a diffuse disease.

DR. CALKINS: Boas and Foley[10] have shown that the hexosamine concentration in the retro-orbital connective tissue of rats is increased after thyroidectomy, provided the pituitary gland is intact. Perhaps composition of the salivary secretions is altered in an analogous manner.

DR. COHEN: Could that be related to thyrotropin activity? The effect of thyrotropin on mucopolysaccharides in tissues is well known.

DR. CALKINS: Yes; it is believed to be related to thyrotropin activity.

CLINICAL DIAGNOSES

?Lupus erythematosus.
Amyloidosis.
Nephrotic syndrome, with peritonitis.
Hemolytic anemia of undetermined cause.
Hypoparathyroidism, surgically induced.
Mikulicz's syndrome.

DR. MAURICE B. STRAUSS'S DIAGNOSES

Generalized systemic amyloidosis.
Underlying systemic disorder: myeloma, lymphoma or lupus erythematosus.
Nephrotic syndrome.
Pulmonary infection and probably infarction.

Hemolytic anemia.
Mikulicz–Sjögren syndrome.
Graves's disease, with post-thyroidectomy hypothyroidism.
Werlhof's disease.

Anatomical Diagnoses

Amyloidosis, with involvement of lymph nodes, salivary glands, skeletal muscle, intestines and lungs.
Thrombosis of vena cava and renal veins, bilateral, with nephrotic syndrome.
Pulmonary emboli and infarcts, recent and old.
Thromboses involving arterioles, venules and capillaries, generalized.
Peritonitis, pneumococcal.
(Acquired hemolytic anemia), with hemosiderosis of accessory spleen.
(Thrombocytopenic purpura).
Splenectomy (twelve years).
Thyroidectomy (six years), for diffuse thyroid hyperplasia.
(Hypothyroidism, postoperative, treated with thyroid).

Pathological Discussion

Dr. Cohen: I must say that I should be as happy to see Virchow here as Dr. Strauss would be to see Osler.

The body was emaciated to the point of cachexia, and chains of lymph nodes in the neck and in the axilla were palpable. The peritoneum contained 1500 ml. of purulent fluid. The pleural cavities also contained fluid. The lungs were studded with infarcts — particularly the lower lobes — that varied in age and undoubtedly accounted for the many episodes of chest pain that the patient had experienced in the preceding years. The most striking part of the gross findings, however, was the massive chains of firm, reddish-brown lymph nodes in the mediastinum and the retroperitoneum. On microscopical examination the tissue of these nodes was replaced by an acidophil amorphous substance, which we, on the basis of staining reaction and distribution, considered to be amyloid. A biopsy of the parotid gland at the time of autopsy revealed an almost complete replacement of the parotid tissue by amyloid. This case must be included now among the cases of Mikulicz's syndrome caused by amyloidosis although it may not have originated as such. Amyloid was also present in small quantities in skeletal muscle, in the intestinal tract and in the lung. The predominant site of amyloid deposition was clearly the reticuloendothelium of the lymph nodes. The bone marrow was normal. The location of the amyloid in this case corresponds to what is usually considered a primary distribution. A 6-gm. accessory spleen found in the left upper quadrant showed extensive hemosiderosis secondary to multiple transfusions and the hemolytic process.

The clinician presented with a case of amyloid disease proved by biopsy in which the nephrotic syndrome develops is almost certain to ascribe the syndrome to amyloidosis of the kidneys. He would be correct in most of the cases; in this case he would be wrong. This patient had a massive thrombosis of the inferior vena cava, which extended into both renal veins. The thrombus was sufficiently organized to have been present for a considerable time and to have produced the nephrotic syndrome. We know, as Dr. Strauss mentioned, that thrombosis of the renal veins can cause nephrosis. It was described by Derow and others[11] in 1939, and quite a number of cases have been reported since, although it is certainly one of the rarer causes of the nephrotic syndrome. The kidney parenchyma was free of amyloid.

In addition to the thrombosis of the large veins, there were scattered throughout the tissues small amorphous thrombi in arterioles, venules and capillaries similar in appearance to the thrombi that have been described as platelet thrombi and are associated with the condition called thrombotic thrombocytopenic purpura. We cannot say that this syndrome was present in this case. Certainly, the clinical and laboratory picture did not suggest it. There were a few of these thrombi in the portal spaces of the liver associated with some inflammatory infiltration. These were rare and, I think, do not account for any liver disease. No other abnormality was present in the liver.

This patient died of pulmonary emboli and of the pneumococcal peritonitis that so frequently complicates nephrosis from any cause. Permission for examination of the brain was not obtained.

Dr. Maloof: Can you say anything about the ovaries and adrenal glands?

Dr. Cohen: The ovaries and the adrenal glands were normal.

Dr. Maloof: Did you not get a piece of the thyroid gland?

Dr. Cohen: Fifty-eight grams of thyroid tissue was removed at the operation. The surgeons said that they left 4 gm. We could not find it.

In attempting to fit the varied clinical and pathological findings in this case into a single framework one must resort to a considerable extent to speculation. This woman had, during the course of the long illness, thrombocytopenic purpura, acquired hemolytic anemia and an abnormality of the serum protein characterized by an elevation of the globulin fraction. Some of the cases of thrombocytopenic purpura and acquired hemolytic anemia are the result of the production of autoimmune antibodies to platelet and red-cell protein. Unfortunately, in this case these were not directly demonstrated; however, a positive Coombs test is quite suggestive in cases of hemolytic

anemia. It is also known that amyloid deposition may be produced by repeated and unusual stimulation of the immune mechanism in laboratory animals by the administration of foreign proteins. There is clinical evidence that some such mechanism may be present in human beings. Morphologically, amyloid is intimately related to the reticuloendothelial system, which is its main site of deposition. Amyloid is associated, as Dr. Strauss has mentioned, with tumors and proliferations of this system and its derivatives. Particularly interesting is the fact that diseases of the reticuloendothelial system are frequently associated with abnormalities of serum protein, production of autoimmune antibodies and other abnormalities of the immune mechanism. Indeed, components of this system are considered by some to be the normal site of production of at least a portion of the immune globulin.

I should like to postulate that this woman's basic disease lay in the reticuloendothelium, perhaps at the level of protein synthesis, and was manifest clinically by the production of abnormal autoimmune antibodies to red cells and platelets. Over a period of years persistent stimulation of this abnormal immune mechanism resulted in the laying down in the reticuloendothelial system of an abnormal protein substance, which we call amyloid.

The possibility that this patient had a "collagen disease," particularly disseminated lupus erythematosus, was repeatedly raised during the course of the many admissions here. Speculating as I am, it can do no more harm to go a bit farther. It is probably naïve to consider that, when abnormal antibodies to red cells and platelets are being produced, the source of origin of these antibodies is necessarily limited to these proteins as stimulating antigens. It is likely that we recognize the syndromes of thrombocytopenic purpura and acquired hemolysis because they are often striking and characteristic clinically, and easily quantitated and confirmed in the laboratory. When autoimmune antibodies to platelets and red cells are being produced, it is conceivable that abnormal antibodies are capable also of being produced and perhaps actually are being formed against other tissues in the body but with more subtle and less easily quantitated clinical manifestations. Perhaps, as many workers believe, in the "collagen diseases" there is an abnormal immune reaction in which tissue proteins act as antigens for autoantibodies accounting for damage to blood vessels and connective tissue. It is interesting that Teilum[12] has related some of the morphologic changes in disseminated lupus, a disease often associated with hemolysis, thrombocytopenia, neutropenia and abnormalities of the serum protein, to amyloid. Amyloid deposition in rheumatoid arthritis is well known. In this patient the characteristic morphologic criteria for the diagnosis of a "collagen disease" were not present, although multiple thromboses of smaller vessels may be found in disseminated lupus. A fundamental relation may exist, however, between the syndrome present in this patient and the "collagen diseases" in a common disturbance of the immune mechanism.

The presence of associated thyrotoxicosis and later hypothyroidism stimulated an investigation of the literature on what we call the hormonology of amyloid; it probably would not be proper to refer to it as the endocrinology of amyloid. It was found that thyrotropin[13] will accelerate the deposition of amyloid to a considerable extent in laboratory animals. One wonders whether during the course of her illness the patient was secreting excessive thyrotropin and, if she was, what effect it had on her amyloid disease. Cortisone[12] was also found to be an accelerator of amyloid deposition. This woman received considerable amounts of this hormone. It would be interesting to determine the effect of long-term cortisone therapy on amyloid deposition in patients with rheumatoid arthritis. The somatotrophic hormone does not stimulate amyloid deposition in the laboratory animal.[13] Thyroid hormone apparently does not, and I am not aware of such an effect of sex hormones.

References

1. Osler, W. Visceral lesions of purpura and allied conditions. *Brit. Med. J.* **1**:517-525, 1914.
2. Morgan, W. S., and Castleman, B. Clinicopathologic study of "Mikulicz's disease." *Am. J. Path.* **29**:471-503, 1953.
3. Morgan, W. S. Probable systemic nature of Mikulicz's disease and its relation to Sjögren's syndrome. *New Eng. J. Med.* **251**:5-10, 1954.
4. Case Records of the Massachusetts General Hospital (Case 39191). *New Eng. J. Med.* **248**:823-828, 1953.
5. Castle, W. B. Personal communication.
6. Teilum, G. Allergic hyperglobulinosis and hyalinosis (paramyloidosis) in reticulo-endothelial system in Boeck's sarcoid and other conditions: morphologic immunity reaction. *Am. J. Path.* **24**:389-408, 1948.
7. Zinneman, H. H., and Hall, W. H. Recurrent pneumonia in multiple myeloma and some observations on immunologic response. *Ann. Int. Med.* **41**:1152-1163, 1954.
8. Fawcett, D. M., and Kirkwood, S. Role of salivary glands in extrathyroidal iodine metabolism. *Science* **120**:547, 1954.
9. Tong, W., Potter, G. D., and Chaikoff, I. L. Notes and comments: concerning role of salivary gland in metabolism of intravenously injected diiodotyrosine. *Endocrinology* **57**:636-638, 1955.
10. Salas, P. L., and Foley, J. B. Regulation of connective tissue hexosamine levels by anterior pituitary and thyroid glands. *Proc. Soc. Exper. Biol. & Med.* **87**:89-91, 1954.
11. Derow, H. A., Schlesinger, M. J., and Savitz, H. A. Chronic progressive occlusion of inferior vena cava and renal and portal veins, with clinical picture of nephrotic syndrome: report of case, with review of literature. *Arch. Int. Med.* **63**:626-647, 1939.
12. Teilum, G. Cortisone-ascorbic acid interaction and pathogenesis of amyloidosis, mechanism of action of cortisone on mesenchymal tissue. *Ann. Rheumat. Dis.* **11**:119-135, 1952.
13. Unto, U., Peräsalo, O., and Vapaavuori, M. Effect of growth hormone and thyrotropin on caseinate amyloidosis. *Acta pathol. et microbiol. Scandinav.* **37**:322-328, 1955.

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FLAVONOID, THAT IS

IN recent years of plenty if not of peace a thoroughly up-to-date sales technic has evolved to launch a new pharmaceutical preparation directly at the American people with only a passing nod at the medical profession on the way by. The technic itself is simple enough — it is a business version of don't fire till you see the whites of their eyes and then let them have it. It involves a mass blast at a gullible public by newspapers, radio and television. People who have retired the day before with an unsophisticated faith in old things and old ways awake to find that all is changed. Detergents have replaced soap; plant activators have arrived to do what the rain and sun did so feebly; and plasticized panes have made storm windows a cumbersome thing of the past. From a business point of view this is a reasonable way of introducing a new product; it is the way some of the luxuries of modern life were born.

A disturbing note arises, however, when the "D day" technic is brought into the area of medicine and pharmaceutics. Since it is purposely designed to overwhelm customer sales-resistance it must dispose of the advance outposts of the medical profession. From a business point of view physicians can be easily outsmarted: they are simply to be by-passed like whiskered veterans guarding the vestiges of a Maginot Line that doesn't really count for those in the know.

One of the most spectacular examples of the rocket technic in medical advertising announced the arrival of the antihistamines. Any doctor who didn't have a knowing look on his face when he was told about them at a cocktail party — having been too busy to read the morning newspaper or the new *Reader's Digest* — was something of a relic. "But my dear, they're wonderful. I'm always due for a cold by this time." The antihistamines were ideal products for slick merchandising methods.

The new refinement used recently to launch another cold cure called for the use of a Nobel Prize winner and implied that his research resulted directly in the conquest of this common affliction. A final bit of tinsel calculated completely to disarm the by now bewildered family physician was the part of the advertisement advising the customer to ask his doctor about the new remedy: "He knows that unlike Antihistamines and so-called miracle drugs which have sometimes caused unpleasant side-effects such as drowsiness, upset stomach, dizzy spells or skin rashes," the ingredients of the new compound "have been conclusively proven to be absolutely safe and free from ill effects." This degree of combined safety with a pain killer and an anti-virus factor results in a remedy beyond ordinary belief.

It was practices of which this campaign is reminiscent that in the past led to the promulgation of statutes and ordinances culminating in the Food, Drug and Cosmetics Act and similar restrictive and

regulatory machinery. The time is approaching when it will become necessary to take another hard look at the situation as it is developing and attempt to apply some effective remedies to protect both the profession and the public before an era of therapeutic chaos is reached. But the greater tragedy of these developments is their reflection on the attitudes and leadership of both business and the not entirely unknowledgeable lay press.

Both medicine and the sniffles may be expected to survive the impact of a new cold cure, since, as with measles, the prognosis is good. It is the steady prostitution of due process that needs to be eyed coldly and pondered by the profession, and if there is a stand to be taken it is by physicians themselves.

WHERE CHARITY BEGINS

THE membership of the Massachusetts Medical Benevolent Society, composed entirely of fellows of the Massachusetts Medical Society, has increased by over 50 per cent during the fiscal year. Lest the fellows of the Massachusetts Medical Society, however, constituting the group that is eligible for membership in the Benevolent Society, should become excessively proud of this achievement, it should be brought out that the net increase of 68 represents a total accession of but 75 new members, and a total membership of only 201. They have been gleaned from the list of over 7000 who would be welcomed as participants in this basic philanthropy.

The Benevolent Society, as has been mentioned in these pages at various times during the past century, grew out of a meeting of the Boston Medical Book Club held in December, 1856. These responsible physicians were concerned over the financial plight of certain of their professional colleagues and their families, and organized the Society, which held its first meeting on March 19, 1857, and dates its existence from that time. It accumulated a modest endowment and each year since its beginning has brought financial aid to those members of the profession who were found to be in actual want. In 1954, for example, $9,071 was disbursed to 22 different beneficiaries in quarterly payments of from $15 to $300.

The Massachusetts Medical Society gave official recognition to this small, benevolent-minded group within its membership, and the function it has been performing, by the establishment in 1948 of a committee on benevolence. This committee has been allowed an annual appropriation, which has been dispensed as needed through the agency of the Benevolent Society.

The Benevolent Society, however, needs more than a handout from the Medical Society to augment its own modest resources. It needs official "benefactors," who achieve this high distinction by the donation of $500, life members who become such on the payment of $200 in a lump sum, and many annual members whose $5 dues each year will not only swell the available funds by that sum but also testify to the member's interest in such a benevolence. For, as has been intimated before this, the gift without the giver may be bare indeed.

It seems little enough to expect that the Benevolent Society's hundredth year should be marked by a membership of 1000 — 1 out of 7 of the members of the Massachusetts Medical Society instead of 1 out of every 35!

A note published in last week's issue of the *Journal* tells in one easy lesson how to become a member of the Massachusetts Medical Benevolent Society.

RESEARCH IN NURSING

WELCOME indeed is the recent announcement by the United States Public Health Service of grants and fellowships for postgraduate training in research into means of improving the quality and increasing the availability of nursing care. Most of the $625,000 allotted for this program will go for research grants, but the portion earmarked for the fellowships will make possible graduate study and special training of nurses in research methods. The three recipients of the current fellowships will investigate parent-child relations (in a study with the Committee on Human Development of the University of Chicago), comparative changes in attitude of nursing and liberal-arts students toward their respective courses of study and legal responsibility of nurses.

The Department of Health, Education and Welfare thus gives special attention to the nursing profession in its over-all planning to meet the shortcomings in the medical and public-health needs of the nation. This valuable addition to the Government's health program cannot fail to receive the enthusiastic endorsement of the medical profession and the public alike.

CARDIOLOGISTS POLLED

OPINIONS, mainly derogatory, have already been expressed regarding the poll of American cardiologists conducted for *U. S. News & World Report* on the subject of President Eisenhower's physical fitness for a second term. The questionnaire is reported to have been sent to all cardiologists listed as such in the *Directory of Medical Specialists;* as of January 6, 275 had replied, many of them before they realized that they were being trapped into giving a categorical opinion on a patient whom they had never seen and on whose case they had never been asked in consultation. The opinions, moreover, were quite obviously intended for publication, a further violation of what

many would consider the highest ethical standards of the profession.

The results of the poll were published in *U. S. News & World Report* on January 13 "as a public service." Their publication may be considered as actually representing a disservice not only to those who answered the questionnaire, but to the public in whose minds may be planted unjustifiable ideas, one way or the other, regarding the President's future fitness for office.

Even the fact that the poll concerns so public a figure as the President can scarcely condone its unfortunate implications, especially in view of its lack of real significance. Of questionable value, it was in unquestionably bad taste; nor does this mild indictment take into consideration its fundamentally cruel aspects.

The value of cider as a prophylactic of cholera, has been discussed in our pages, and we notice that a correspondent of the Medical Times and Gazette suggests the use of cider and its cognate beverage, perry, by individuals of a gouty diathesis, believing that the malic acid, like the citric, would aid in eliminating the free lithic acid from the system.

Boston M. & S. J., *February 7, 1856*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

DUMAS — Charles E. Dumas, M.D., of Worcester, died on December 9. He was in his fifty-sixth year.

He received his degree from Boston University School of Medicine in 1926. He was chief of the Department of Radiology at Worcester City Hospital and a member of the staffs of Fairlawn and Milford hospitals and was a member of the New England Roentgen Ray Society.

He is survived by his widow, three brothers, four sisters, and a stepdaughter.

FRANZ — Adolph Franz, M.D., of Holyoke, died on November 22. He was in his ninety-fourth year.

He received his degree from Columbia University College of Physicians and Surgeons in 1887. He was a fellow of the American Medical Association and the American College of Surgeons and a member of the Springfield Academy of Medicine.

He is survived by his widow, two sons and three daughters.

RAYMOND — Albert O. Raymond, M.D., of Worcester, died on December 13. He was in his sixty-sixth year.

He received his degree from Tufts College Medical School in 1914. He was formerly senior obstetrician at Worcester City Hospital and was a fellow of the American Medical Association.

He is survived by his widow.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR DECEMBER, 1955

RÉSUMÉ

DISEASE	DEC. 1955	DEC. 1954	SEVEN-YEAR MEDIAN
Chancroid	1	1	1
Chicken pox	927	1317	1450
Diphtheria	0	5	5
Dog bite	625	667	656
Dysentery, bacillary	2	18	7
Encephalitis, infectious	2	4	3
German measles	58	119	83
Gonorrhea	169	204	186
Granuloma inguinale	0	1	0
Hepatitis, infectious	19	106	60*
Lymphogranuloma venereum	0	2	1
Malaria	0	0	0
Measles	167	6752	199
Meningitis, meningococcal	11	5	7
Meningitis, Pfeiffer bacillus	4	4	4
Meningitis, pneumococcal	7	1	3
Meningitis, staphylococcal	0	0	0
Meningitis, streptococcal	0	0	0
Meningitis, undetermined	7	10	6
Mumps	175	1526	1288
Poliomyelitis	53	33	24
Salmonellosis	36	22	4
Scarlet fever	227	319	371
Syphilis	114	123	123
Trichinosis	0	1	2
Tuberculosis, pulmonary	194	219	201
Tuberculosis, other forms	5	21	11
Typhoid fever	3	0	1
Undulant fever	0	1	1
Whooping cough	77	317	317

*Six-year median.

COMMENT

Diseases below the seven-year median were chicken pox, diphtheria, bacillary dysentery, German measles, infectious hepatitis, measles, mumps, scarlet fever and whooping cough.

During December mumps was at the lowest level for this month since 1918.

By a single case scarlet fever during December was at the lowest level for this month in the State's history.

By a considerable margin whooping cough during December was at the lowest level for this month in the history of the State.

Diseases above the seven-year median were poliomyelitis, salmonellosis, and typhoid fever.

During December salmonellosis was at the highest level for this month in the history of the State.

GEOGRAPHIC DISTRIBUTION OF CERTAIN DISEASES

The following diseases were reported from the communities named:

Dysentery, bacillary: Boston, 1; Newton, 1; total, 2.

Encephalitis, infectious: Norwood, 1; West Springfield, 1; total, 2.

Hepatitis, infectious: Arlington, 1; Boston, 3; Chelmsford, 1; Danvers, 1; Fall River, 1; Gloucester, 1; Haverhill, 1; Huntington, 1; Lowell, 1; Medford, 1; Milton, 1; Natick, 1; Revere, 1; Rockport, 1; Somerville, 1; Springfield, 2; total, 19.

Meningitis, meningococcal: Boston, 6; Fall River, 1; New Bedford, 1; Plymouth, 1; Watertown, 1; Worcester, 1; total, 11.

Meningitis, Pfeiffer bacillus: Kingston, 1; Norwood, 1; Somerville, 1; Weymouth, 1; total, 4.

Meningitis, pneumococcal: Chelsea, 1; Holyoke, 1; Lynn, 1; Quincy, 1; Shrewsbury, 1; Worcester, 2; total, 7.

Meningitis, undetermined: Barnstable, 1; Boston, 1; Hingham, 1; Newton, 1; Reading, 1; Springfield, 1; Tewksbury, 1; total, 7.

Poliomyelitis: Amherst, 1; Arlington, 2; Attleboro, 1; Barnstable, 1; Bellingham, 1; Billerica, 1; Blackstone, 2; Boston, 1; Brockton, 3; Charlemont, 1; Chicopee, 1; Concord, 3; Dartmouth, 2; Fall River, 1; Falmouth, 1; Gloucester, 1; Harwich, 1; Holden, 1; Holyoke, 1; Hudson, 1; Leicester, 1; Leominster, 1; Lynn, 1; Lynnfield, 1; Marl-

boro, 1; Millville, 1; Newton, 1; No. Attleboro, 1; Oxford, 1; Peabody, 1; Quincy, 1; Randolph, 1; Reading, 1; Spencer, 1; Springfield, 1; Waltham, 1; Wareham, 1; Watertown, 1; Wellesley, 1; Weymouth, 2; Whitman, 3; Worcester, 2; total, 53.

Salmonellosis: Beverly, 1; Boston, 5; Fitchburg, 1; Harvard, 1; Lynn, 2; Milton, 2; Newton, 1; Peabody, 1; Salem, 1; Saugus, 1; Somerville, 4; Springfield, 2; Stoughton, 1; Swampscott, 4; Upton, 1; Waltham, 1; Watertown, 2; Wellesley, 1; Weston, 1; Woburn, 1; Worcester, 2; total, 36.

Tetanus: Brockton, 1; Revere, 1; total, 2.

Typhoid fever: Brookline, 1; Lowell, 1; Westport, 1; total, 3.

CORRESPONDENCE

ARTHRITIS AND RHEUMATISM FOUNDATION

To the Editor: Arthritis, particularly the rheumatoid and gouty types, has always puzzled both specialists and general practitioners. The advent of corticosteroids and other modern therapies has contributed to palliative treatment only. It is obvious, therefore, that the interest of physicians in all aspects of medical research and practice must be stimulated if a definitive approach to the protean manifestations of this widespread malady is to be attained. This has been and continues to be a prime objective of the Arthritis and Rheumatism Foundation.

To implement this major objective the Foundation provides the following resources to qualified physicians: fellowships of variable duration, with stipends to meet individual needs, ranging from brief orientation to the more extensive training required for qualification as rheumatologists or chiefs of arthritis clinics; financial support to research projects and to operating clinics; and guidance and assistance in the establishment of new clinics.

Every physician can contribute to this program by interpreting the objectives to other physicians and to his patients, availing himself of the Foundation's resources and supporting its fund-raising activities.

WILLIAM H. CHASEN, M.D.
Quincy, Massachusetts

LATERAL FILM IN ANEURYSM

To the Editor: In referring to Dr. Crane's excellent article, "Arteriosclerotic Aneurysm of the Abdominal Aorta," in the December 1 issue of the *Journal*, I should like to point out the value of a true lateral film of the abdomen, as well as a standard posteroanterior plain film, not only in the diagnosis of aneurysm but also in defining the extent of the lesion. This was not pointed out in Dr. Crane's article or the references he cited, and is not generally known or appreciated by either clinicians or radiologists. This simple study has been very helpful in our hands.

ELLIS P. SINGER,
First Lieutenant USAF (MC)
Chief, Outpatient Clinic
3275th USAF Hospital
Parks Air Force Base
California

SUSPENSION OF LICENSE

To the Editor: At the meeting of the Board of Registration in Medicine held December 15, 1955, it was voted to suspend the registration of Dr. Anthony A. Forziati, of Boston, for six months beginning January 1, 1956.

ROBERT C. COCHRANE, M.D., *Secretary*
Board of Registration in Medicine
State House
Boston

BOOK REVIEW

Klinische Elektropathologie. I. *Kritische Sammlung elektropathologischer Gutachten aus interner Sicht.* By Dr. med. habil. S. Koeppen. II. *Die Neurologie des elektrischen Unfalls und des Blitzschlags: Mit einem Kapitel über die elektromagnetischen Wellen und die Atomkräfte.* By Prof. Dr. F. Panse. 8°, cloth, 424 pp., with 60 illustrations and 3 tables. Stuttgart: Georg Thieme, 1955. (Distributed in the United States by the Intercontinental Medical Book Corporation, New York City.) $7.85.

The book is divided into two parts: a discussion of the internal changes associated with electric accidents and a study of the related neuropathologic changes. This is a full and complete study with many illustrations. An excellent discussion of lightning is included, as well as a careful discussion of electric accidents. This book could be of special interest to medicolegal pathologists and to industrial physicians. There is a very good European bibliography. The work will be of chief value from the standpoint of a reference.

SHIELDS WARREN, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this list must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Biochemistry: An introductory textbook. By Felix Haurowitz, Dr. med. (Prague), Dr. rer. nat. (Prague), professor of chemistry, Indiana University. 8°, cloth, 485 pp., with illustrations and tables. New York: John Wiley and Sons, Incorporated, 1955. $6.75.

Semi-Micro Organic Preparations. By J. H. Wilkinson, B.Sc., Ph.D., F.R.I.C. 12°, cloth, 94 pp., with 23 illustrations. Springfield, Illinois: Charles C Thomas, 1955. $2.00.

Man in a Cold Environment: Physiological and pathological effects of exposure to low temperatures. By Alan C. Burton, Ph.D., professor of biophysics, University of Western Ontario; and Otto G. Edholm, M.B., head of Division of Human Physiology, National Institute for Medical Research, Medical Research Council, England. 8°, cloth, 273 pp., with 75 illustrations. London: Edward Arnold, Limited, 1955. $6.75. (Distributed by Williams and Wilkins, Baltimore.) (No. 2, *Monographs of the Physiological Society.*)

Atlas der Haut-und Geschlechtskrankheiten. By Prof. Dr. Walter Frieboes, professor and director, Universitäts-Hautklinik, Berlin; and Dr. Walther Schönfeld, professor and superintendent, Universitäts-klinik und Poliklinik für Haut- und Geschlechtskrankheiten, Heidelberg. 4°, cloth, 292 pp., with 469 illustrations. Stuttgart: Georg Thieme, 1955. $28.10. (Distributed in the United States by the Intercontinental Medical Book Corporation, New York City.)

The Work of WHO, 1954. Annual Report of the Director-General to the World Health Assembly and to the United Nations. 4°, paper, 209 pp., with illustrations, 2 tables and 4 maps. Geneva: World Health Organization, 1955. $2.00. (No. 59, *Official Records of the World Health Organization.*)

Kreislaufregulation: Eine physiologische, pathophysiologische und klinische Studie. By Prof. Dr. H. Reindell, Dr. E. Schildge, Dr. H. Klepzig and Dr. H. W. Kirchhoff, Freiburg/Br. With a foreword by Prof. Dr. Ludwig Heilmeyer, Freiburg/Br. 8°, cloth, 315 pp., with 69 illustrations. Stuttgart: Georg Thieme, 1955. $9.40. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

Transactions of the American Goiter Association: 1954 annual session, April 29, 30 and May 1, 1954, Somerset Hotel, Boston, Massachusetts. 4°, cloth, 483 pp., with illustrations and tables. Springfield, Illinois: Charles C Thomas, 1955. $14.00.

Clues in the Diagnosis and Treatment of Heart Disease. By Paul D. White, M.D. 8°, cloth, 186 pp., with 35 illustrations. Springfield, Illinois: Charles C Thomas, 1955. $5.50. (Publication No. 242, *American Lecture Series.*)

Management of Addictions. Edited by Edward Podolsky, M.D., Department of Psychiatry, Kings County Hospital, Brooklyn. 8°, cloth, 413 pp., with illustrations. New York: Philosophical Library. $7.50.

Demonstrations of Physical Signs in Clinical Surgery. By Hamilton Bailey, F.R.C.S. (Eng.), F.R.S.E., general surgeon, Metropolitan Ear, Nose and Throat Hospital, consulting surgeon, Italian Hospital, Hunterian Professor, Royal College of Surgeons, and vice-president, International College of Surgeons; assisted by Allan Clain, M.B. (Capetown), F.R.C.S. (Eng.), senior surgical registrar, Royal Cancer Hospital, London. Twelfth edition. 8°, cloth, 456 pp., with 681 illustrations. Baltimore: Williams and Wilkins, 1954. $8.00.

1955 Medical Progress: A review of medical advances during 1954. Edited by Morris Fishbein, M.D. 8°, cloth, 346 pp. New York: Blakiston Division, McGraw-Hill Book Company, Incorporated, 1955. $5.00.

Blutkrankheiten: Methodik, Klinik und Therapie. By Professor Dr. Hanns Fleischhacker. 8°, cloth, 247 pp., with 76 partly-colored illustrations. Vienna: Wilhelm Maudrich, 1955. $7.50. (Distributed in America by Intercontinental Medical Book Corporation, New York City.)

Letalfaktoren: In ihrer Bedeutung für Erbpathologie und Genphysiologie der Entwicklung. By Ernst Hadorn, professor of zoology and comparative anatomy, Universität Zürich. 8°, cloth, 338 pp., with 129 illustrations. Stuttgart: Georg Thieme, 1955. DM 39.-($9.30). (Distributed in America by Intercontinental Medical Book Corporation, New York City.)

Diseases of the Thyroid Gland. By Samuel L. Gargill, M.D., assistant clinical professor of medicine, Harvard Medical School, and visiting physician, consultant to Endocrine Clinic and head of the Fertility Clinic, Beth Israel Hospital, Boston; and Mark Falcon Lesses, M.D., instructor in medicine, Harvard Medical School, and visiting physician, chief of Endocrine Clinic, and director of Blood Bank, Beth Israel Hospital, Boston. 8°, cloth, 500 pp., with 68 illustrations. New York: Oxford University Press, 1955. $12.00. (Reprinted from *Oxford Loose-Leaf Medicine.*)

Shearer's Manual of Human Dissection. Edited by Charles E. Tobin, Ph.D., associate professor of anatomy, University of Rochester School of Medicine and Dentistry. Third edition. 4°, cloth, 287 pp., with 79 illustrations. New York: Blakiston Division, McGraw-Hill Book Company, Incorporated, 1955. $6.00.

The Care of Your Skin. By Herbert Lawrence, M.D. 12°, cloth, 95 pp., with illustrations. Boston: Little, Brown and Company, 1955. $2.50.

Cardiac Emergencies and Heart Failures: Prevention and treatment. By Arthur M. Master, M.D., cardiologist, Mount Sinai Hospital, New York City, and associate clinical professor of medicine, Columbia University College of Physicians and Surgeons; Marvin Moser, M.D., assistant physician in medicine, Montefiore Hospital, New York City, and adjunct physician in medicine (cardiology), Grasslands Hospital, Valhalla, New York; and Harry L. Jaffe, M.D., assistant attending physician in cardiology, Mount Sinai Hospital, New York City, and lecturer in medicine, Columbia University College of Physicians and Surgeons. Second edition, thoroughly revised. 12°, cloth, 203 pp., with 14 illustrations. Philadelphia: Lea and Febiger, 1955. $3.75.

Practical Endocrinology. By Lewis M. Hurxthal, M.D., head, Department of Internal Medicine, Lahey Clinic. In co-operation with A. Seymour Parker, M.D., physician, Department of Internal Medicine, Lahey Clinic; and Hirsh Sulkowitch, M.D., research associate, Lahey Foundation. 8°, cloth, 318 pp., with 17 illustrations and 4 tables. New York: Landsberger Medical Books, Incorporated, 1955. $7.00. (Distributed by Blakiston Division, McGraw-Hill Book Company, Incorporated, New York City.)

The Clinical Interview. Vol. 2. *Therapy: A method of teaching sector psychotherapy.* By Felix Deutsch, M.D., and William F. Murphy, M.D. 8°, cloth, 335 pp., with charts. New York: International Universities Press, Incorporated, 1955. $7.50.

The Coagulation of Blood: Methods of study. Edited by Leandro M. Tocantins, M.D., professor of clinical and experimental medicine and director, Charlotte Drake Cardeza Foundation, Jefferson Medical College, and attending physician, Jefferson Hospital, Philadelphia. 8°, cloth, 240 pp., with illustrations and tables. New York: Grune and Stratton, 1955. $5.75.

Angiographic Localization of Intracranial Masses. By Arthur Ecker, M.D., Ph.D., State University of New York, Upstate Medical Center, Syracuse Memorial Hospital; and Paul A. Riemenschneider, M.D., State University of New York, Upstate Medical Center, Syracuse Memorial Hospital. 8°, cloth, 433 pp., with 413 illustrations. Springfield, Illinois: Charles C Thomas, 1955. $13.50.

Antimicrobial Therapy in Medical Practice. By Harrison F. Flippin, M.D., associate professor of clinical microbiology, Graduate School of Medicine, University of Pennsylvania, visiting physician, Philadelphia General Hospital (Blockley Division), and chief, Section of Infectious Diseases, Department of Medicine, School of Medicine, University of Pennsylvania; and George M. Eisenberg, D.Sc., associate in medicine, Graduate School of Medicine, University of Pennsylvania, and chief, Division of Bacteriology and Immunology, Department of Laboratories, Philadelphia General Hospital (Blockley Division). 8°, cloth, 284 pp., with 11 tables. Philadelphia: F. A. Davis Company, 1955. $5.00.

Heart Disease: Its diagnosis and treatment. By Emanuel Goldberger, M.D., associate attending physician, Montefiore Hospital, New York City, cardiologist and attending physician, Lincoln Hospital, New York City, consulting cardiologist, St. Joseph's Hospital, Yonkers, New York, and lecturer in medicine, Columbia University College of Physicians and Surgeons. Second edition, thoroughly revised. 8°, cloth, 781 pp., with 107 illustrations and 5 tables. Philadelphia: Lea and Febiger, 1955. $12.50.

Kinesiology of the Human Body: Under normal and pathological conditions. By Arthur Steindler, M.D., (Hon.) F.R.C.S., Eng., F.A.C.S., F.I.C.S., professor of orthopedic surgery, emeritus, State University of Iowa, and head, Orthopaedic Department, Mercy Hospital, Iowa City. 4°, cloth, 708 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1955. $19.75.

Pathology. By Peter A. Herbut, M.D., professor of pathology, Jefferson Medical College, and director of Clinical Laboratories, Jefferson Medical College Hospital, Philadelphia. 4°, cloth, 1227 pp., with 1378 illustrations and 6 color plates. Philadelphia: Lea and Febiger, 1955. $16.00.

Congenital Malformations and Birth Injuries: A handbook on nursing. By Jessie Stevenson West, R.N., P.T. 12°, paper, 178 pp., with 30 illustrations. New York: Association for the Aid of Crippled Children, 1954. $1.00.

Neuropharmacology: Transactions of the first conference May 26, 27 and 28, 1954, Princeton, New Jersey. Edited by Harold A. Abramson, M.D., assistant clinical professor of physiology, Columbia University College of Physicians and Surgeons, and associate attending physician for allergy, Mt. Sinai Hospital, New York City. 8°, cloth, 210 pp., with 44 illustrations and 15 tables. New York: Josiah Macy, Jr., Foundation, 1955. $4.25.

The Yearbook of Psychoanalysis. Vol. 10 (1954). Managing editor, Sandor Lorand, M.D. 8°, cloth, 277 pp. New York: International Universities Press, Incorporated, 1955. $7.50.

Physicians' Office Attendants Manual. Part 1. *Section for Office Work.* By Henry B. Gotten, M.D., associate professor of medicine, University of Tennessee College of Medicine. Part 2. *Section for Laboratory Work.* By Douglas H. Sprunt, M.D., professor of pathology, University of Tennessee College of Medicine. 8°, cloth, 93 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1955. $3.75.

Gynaecology. By Douglas H. MacLeod, M.S. (Lond.), F.R.C.P. (Lond.), F.R.C.S. (Eng.), F.R.C.O.G., gynecologic surgeon, St. Mary's Hospital, consulting surgeon, Queen Charlotte's Maternity Hospital, gynecologic surgeon, Royal Marsden Hospital (Royal Cancer Hospital) and Putney Hospital, and examiner in obstetrics and gynecology, University of Cambridge and Royal College of Obstetricians and Gynaecologists; and Charles D. Read, M.B. (N.Z.), F.R.C.S. (Eng. & Ed.), F.R.A.C.S., F.R.C.O.G., director, Institute of Obstetrics and Gynaecology, British Postgraduate Medical Federation, University of London, senior surgeon, Chelsea Hospital for Women, surgeon, Queen Charlotte's Maternity Hospital and Department of Obstetrics and Gynaecology, Hammersmith Hospital, and external examiner, University of Glasgow. With a section on anatomy by James Snyder, M.D., F.R.C.S.; and a section on physiology and endocrinology by Russell Fraser, M.D., F.R.C.P., reader in medicine, University of London (Postgraduate Medical School of London). Fifth edition. 4°, cloth, 864 pp., with 551 illustrations. Boston: Little, Brown and Company, 1955. $16.00.

Cerebral Vascular Diseases: Transactions of a conference held under the auspices of the American Heart Association, Princeton, New Jersey, January 24-26, 1954. Irving S. Wright, M.D., chairman; and E. Hugh Luckey, editor. 4°, cloth, 167 pp., with 5 tables. New York: Grune and Stratton, Incorporated, 1955. $5.50.

Ancient Therapeutic Arts: The Fitzpatrick Lectures delivered in 1950 and 1951 at the Royal College of Physicians. By William Brockbank, M.A., M.D. (Camb.), F.R.C.P. 8°, cloth, 162 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1955. $5.00.

Essentials of Orthopaedics. By Philip Wiles, M.S. (Lond.), F.R.C.S. (Eng.), senior orthopedic surgeon, Middlesex Hospital, London, and King Edward Memorial Hospital, Ealing, and lecturer in orthopedic surgery, University of London. Second edition. 8°, cloth, 538 pp., with 393 illustrations and 7 colored plates. Boston: Little, Brown and Company, 1955. $10.00.

NOTICES

ANNOUNCEMENT

Dr. Morris Yorshis announces the removal of his office to 158 Main Street, Andover, Massachusetts, for the practice of neurology and psychiatry.

BOSTON GASTROENTEROLOGY SOCIETY

A meeting of the Boston Gastroenterology Society will be held in the Cheever Amphitheater, Boston City Hospital, on Wednesday, February 8, at 8:15 p.m. Dr. David Dreiling will speak on the subject "Pancreatic Disease — Diagnostic Approach," and Dr. Henry Janowitz will discuss the clinical varieties.

HARVARD SCHOOL OF PUBLIC HEALTH FORUM

A forum on the subject "International Problems in Nursing," sponsored by the Harvard School of Public Health, will be held in the auditorium of the Jimmy Fund Building, Children's Medical Center, on Monday, February 13, at 5 p.m.

The forum will be given by Miss Olive Baggallay, M.B.E., LL.B., S.R.N., of London, England. Miss Baggallay was chief nurse of the World Health Organization from 1947 to 1955. From 1944 to 1946 she was chief nurse of the Greek Mission, United Nations Relief and Rehabilitation Administration. Previously, she was executive director of the Florence Nightingale International Foundation.

BENJAMIN WATERHOUSE MEDICAL HISTORY SOCIETY

A dinner meeting of the Benjamin Waterhouse Medical History Society of Boston University School of Medicine will be held in the Musket Room of the Howard Johnson Restaurant at 870 Massachusetts Avenue and Southampton Street, Roxbury, on Monday, February 27, at 6 p.m. The program is scheduled for 7:30, when Professor Arthur Lassek will speak on the subject "Notes on J. Hughlings Jackson."

NEW ENGLAND CARDIOVASCULAR SOCIETY

A meeting of the New England Cardiovascular Society will be presented by the Massachusetts Memorial Hospitals and the New England Center Hospital in Morse Auditorium, Museum of Science, Science Park, Boston, on Monday, February 13, at 8 p.m.

PROGRAM

Massachusetts Memorial Hospitals, Robert W. Wilkins, M.D., presiding:

Cigarette Smoking and Blood Flow in the Foot. John W. Eckstein, M.D., and J. Edwin Wood, M.D.

Myocardial Anoxia in the Normal Heart. William E. Huckabee, M.D.

Comparative Effects of Rubidium and Potassium on the Normal Electrocardiogram. Arthur S. Kunin, M.D., Belton A. Burrows, M.D., Earl H. Dearborn, Ph.D., and Arnold S. Relman, M.D.

Studies with Serotonin and Antiserotonins in Man. William Hollander, M.D., Alan L. Michelson, M.D., and Robert W. Wilkins, M.D.

New England Center Hospital, Samuel Proger, M.D., presiding:

Further Observations Concerning Cholesterol Exchange in the Gastrointestinal Tract. Samuel Cheng, M.D., and Malcolm Stanley, M.D.

The Influence of Electrolyte Changes on the Effects of Antiarrhythmic Drugs: Some preliminary observations. Byron B. Clark, Ph.D.

Ammonium Chloride Intoxication in Congestive Heart Failure. William B. Schwartz, Jr., M.D.

Physicians and medical students are invited.

HARTFORD MEDICAL SOCIETY

The spring program for the Hartford Medical Society is as follows:

February 6. Surgical Treatment of Coronary Insufficiency. Claude Beck.
February 20. Surgical Aspects of Upper Gastrointestinal Bleeding. Ralph Colp.
March 5. Modern Technics in X-Ray Diagnosis. Benjamin Felson.
March 19. Current Concepts of Heart Failure. Eugene Stead.
April 2. Medical Aspects of Bone Disease. I. Snapper.
April 16. Ulcerative Colitis. A. F. R. Andressen.

YALE UNIVERSITY SCHOOL OF MEDICINE

A meeting of the Arthritis Study Unit will be held in the Fitkin Amphitheater, Yale University School of Medicine, on Thursday, February 16, at 3:30 p.m. Dr. Charles O. Bechtol will speak on the subject "Clinical Applications of Bone Physiology."

SOCIETY MEETINGS AND CONFERENCES

FEBRUARY 3. Yale University School of Medicine. Yale-New Haven Medical Center. Page 1092, issue of December 15.
FEBRUARY 6–8. First Regional Standard Nomenclature Institute. Page 192, issue of January 26.
FEBRUARY 6, 20; MARCH 5, 19; APRIL 2 and 16. Hartford Medical Society. Notice above.
FEBRUARY 8. Boston Gastroenterology Society. Page 241.
FEBRUARY 8; MARCH 19–28 and JUNE 4–13. Army Medical Service Postgraduate Course. Page 84, issue of July 14.
FEBRUARY 13. Harvard School of Public Health Forum. Page 241.
FEBRUARY 13. New England Cardiovascular Society. Page 241.
FEBRUARY 13–16. American College of Surgeons. Page 1136, issue of December 22.
FEBRUARY 14. Harvard Medical Society. Page 44, issue of January 5.
FEBRUARY 16. Yale University School of Medicine. Notice above.
FEBRUARY 16; MARCH 28 and APRIL 18. Greater Boston Medical Society. Page 208, issue of August 4.
FEBRUARY 20–22. Atlanta Graduate Medical Assembly. Page 1136, issue of December 22.
FEBRUARY 27. Benjamin Waterhouse Medical History Society. Page 241.
FEBRUARY 29; MARCH 21 and APRIL 25. Massachusetts Heart Association. Page 623, issue of October 6.
MARCH 5 and APRIL 2. Fried Lecture Series. Page 535, issue of September 22.
MARCH 15–17. American Orthopsychiatric Association. Page 86, issue of January 12.
MARCH 19–22. American Academy of General Practice. Page 1092, issue of December 15.
MARCH 21 and APRIL 26. Phi Delta Epsilon Fraternity Graduate Club Program. Page 118, issue of July 21.
MARCH 24 and 25. American Psychosomatic Society. Page 260, issue of August 11.
APRIL 3. Third Microcirculatory Conference. Page 139, issue of January 19.
APRIL 23–26. International Academy of Proctology. Page 86, issue of January 12.
MAY 2. Postgraduate Medical Institute. Page 487, issue of September 15.
MAY 3–5. American Goiter Association. Page 348, issue of August 25.
MAY 28–JUNE 1. European Symposium on Vitamin B. Page 578, issue of September 29.
JUNE 21–23. Society of Nuclear Medicine. Page 1092, issue of December 15.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, FEBRUARY 9

THURSDAY, FEBRUARY 9
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Dr. John Spellman and staff. Saint Elizabeth's Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Medical Grand Rounds. Dr. Sylvester McGinn and staff. Saint Elizabeth's Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*11:15 a.m. Thoracic Conference. Pump Oxygenators: Discussion of principle and practice. Dr. Hugh E. Wilson. Main Amphitheater, Peter Bent Brigham Hospital.
*12:00 m. Clinicopathological Conference. Dr. Benjamin Castleman and associates. Pathology Amphitheater, Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Staff Conference. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Orthopedic Clinic. Amphitheater, Peter Bent Brigham Hospital.
5:00 p.m. Case Presentation and Pathological Discussion Followed by a Subject of Special Presentation. Joslin Auditorium, New England Deaconess Hospital.

FRIDAY, FEBRUARY 10
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m. Pediatric Grand Rounds. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*1:00–3:00 p.m. Combined Medical-Surgical Grand Rounds. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*2:00–3:00 p.m. Pathology Conference. Dr. James Graham. Saint Elizabeth's Hospital.
*4:00–6:00 p.m. X-Ray Conference. Dr. Merrill Sosman. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.
*4:30 p.m. Neuroradiologic Conference. X-Ray Conference Room, New England Deaconess Hospital.

SATURDAY, FEBRUARY 11
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Anesthesia Conference. Dr. Benjamin Etsten. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*8:30–9:30 a.m. Surgical Grand Rounds. Drs. Charles G. Child, III, A. J. A. Campbell and staff. First (Tufts) Surgical Service, New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*10:30 a.m. Teaching Ward Rounds. Ward South 2, Free Hospital for Women.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Hematology Conference (Blood Clinic). Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

MONDAY, FEBRUARY 13
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Staff Conference. Child Psychiatry. By appointment. Conference Room (Burnham 7), Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Medical Conference. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.

(Concluded on page xxvi)